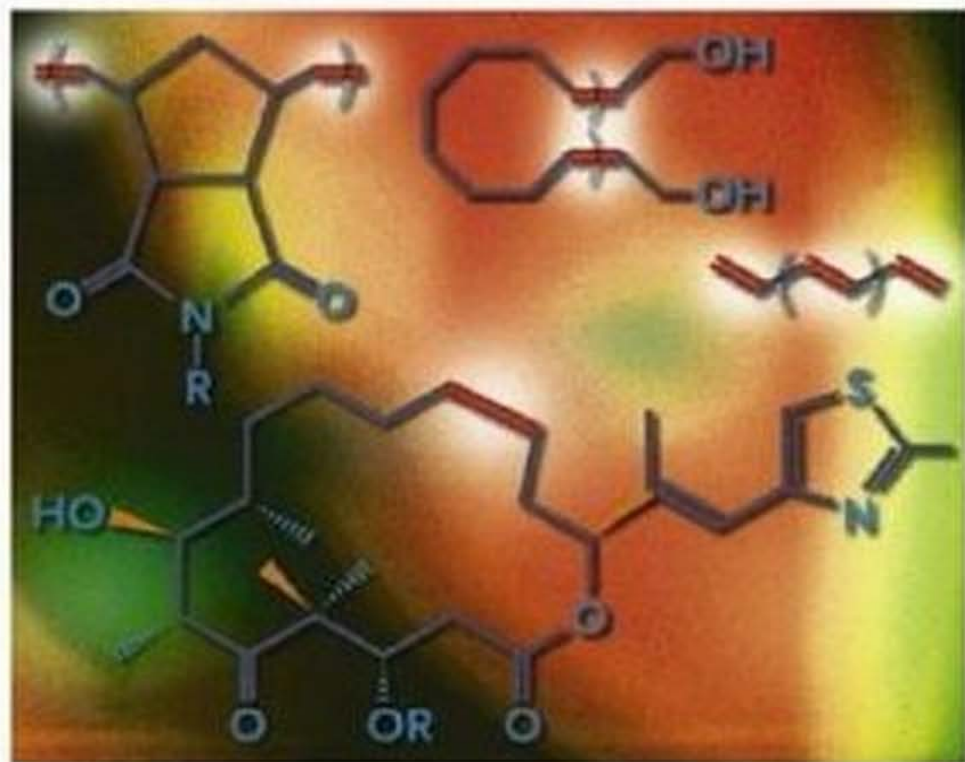


Edited by
Robert H. Grubbs

 WILEY-VCH

Handbook of Metathesis



Robert H. Grubbs (Ed.)
Handbook of Metathesis
Catalyst Development

Handbook of Metathesis

I Volume 1 – Catalyst Development

**| Volume 2 – Applications in Organic
Synthesis**

**| Volume 3 – Applications in Polymer
Synthesis**

Robert H. Grubbs (Ed.)

Handbook of Metathesis

Volume 1 – Catalyst Development

**Volume 2 – Applications in Organic
Synthesis**

**Volume 3 – Applications in Polymer
Synthesis**

Editor

Professor Robert H. Grubbs

Arnold and Mabel Laboratories of Chemical
Synthesis
Division of Chemistry and Chemical
Engineering
California Institute of Technology
Mail Code 164-30, Pasadena, CA 91125
USA

■ This book was carefully produced.
Nevertheless, editor, authors and publisher
do not warrant the information contained
therein to be free of errors. Readers are
advised to keep in mind that statements,
data, illustrations, procedural details or
other items may inadvertently be
inaccurate.

Library of Congress Card No.: applied for

A catalogue record for this book is available
from the British Library.

Bibliographic information published by Die
Deutsche Bibliothek

Die Deutsche Bibliothek lists this
publication in the Deutsche
Nationalbibliografie; detailed bibliographic
data is available in the Internet at [http://
dnb.ddb.de](http://dnb.ddb.de)

© 2003 WILEY-VCH Verlag GmbH & Co.
KGaA, Weinheim

All rights reserved (including those of
translation in other languages). No part of
this book may be reproduced in any form –
by photoprinting, microfilm, or any other
means – nor transmitted or translated into
machine language without written
permission from the publishers. Registered
names, trademarks, etc. used in this book,
even when not specifically marked as such,
are not to be considered unprotected by law.

Printed in the Federal Republic of
Germany.

Printed on acid-free paper.

Typesetting Asco Typesetters, Hong Kong

Printing Strauss Offsetdruck GmbH,
Mörlenbach

Bookbinding J. Schäffer GmbH & Co. KG,
Grünstadt

ISBN 3-527-30616-1

Contents

Volume 1

Preface *xxi*

References *xxv*

List of Contributors *xxvii*

- 1.1 Introduction** *1*
Robert H. Grubbs
References *3*
- 1.2 The Role of the “Tebbe Complex” in Olefin Metathesis** *4*
Robert H. Grubbs
References *6*
- 1.3 The Discovery and Development of High Oxidation State Mo and W Imido Alkylidene Complexes for Alkene Metathesis** *8*
Richard R. Schrock
- 1.3.1 Introduction *8*
- 1.3.2 Tantalum Alkylidene Complexes *9*
- 1.3.3 Early Tungsten Alkylidene Complexes *13*
- 1.3.4 Development of Imido Alkylidene Complexes *15*
- 1.3.5 Rhenium Alkylidene Complexes *20*
- 1.3.6 Details of Reactions of Imido Alkylidene Complexes and Theoretical Calculations *21*
- 1.3.7 Catalyst and Reaction Variations *24*
- 1.3.8 Concluding Remarks *28*
Acknowledgments *28*
References *29*

1.4	From Ill-Defined to Well-Defined W Alkylidene Complexes	33
	<i>Christophe Copéret, Frédéric Lefebvre, and Jean-Marie Basset</i>	
1.4.1	Introduction	33
1.4.2	Oxoalkylidene W Complexes	33
1.4.3	Alkoxy-Alkylidene W Complexes: Kress-Osborn System	35
1.4.4	Aryloxy-Alkylidene W Complexes: Leconte-Basset System	37
1.4.5	Amidoalkylidene W Complexes	38
1.4.6	Imido-Alkylidene W Complexes: Schrock's System	42
1.4.7	Summary and Outlooks	44
	References	45
1.5	Fischer Metal Carbenes and Olefin Metathesis	47
	<i>Thomas J. Katz</i>	
1.5.1	Fischer Metal Carbenes and Olefin Metathesis	47
1.5.2	The Role of Fischer Metal Carbenes in Metathesis	47
1.5.3	Induction of Olefin Metatheses by Fischer Metal Carbenes	49
1.5.3.1	Properties of 2	49
1.5.3.2	Olefin Metatheses Initiated by Metal Carbene 1	49
1.5.3.3	Mechanistic Implications	51
1.5.3.4	Metatheses Initiated by Metal Carbene 2	52
1.5.4	Initiation of Acetylene Polymerization by Fischer Metal Carbenes	53
1.5.4.1	Introduction	53
1.5.4.2	Examples of Acetylene Polymerizations Initiated by Fischer Metal Carbenes	54
1.5.5	Actuation of Olefin Metathesis by Acetylenes	55
1.5.5.1	Metatheses of Cyclic and Acyclic Alkenes Actuated by An Acetylene	55
1.5.5.2	Reaction of Enynes With Fischer Metal Carbenes	55
1.5.5.3	Rearrangement of Enynes to Dienes	56
	References	57
1.6	The Discovery and Development of Well-Defined, Ruthenium-Based Olefin Metathesis Catalysts	61
	<i>SonBinh T. Nguyen and Tina M. Trnka</i>	
1.6.1	The Discovery of Well-Defined Ruthenium Olefin Metathesis Catalysts: A Personal Account by SonBinh Nguyen	61
1.6.1.1	$(PPh_3)_2Cl_2Ru=CH-CH=CPh_2$, the First Well-Defined, Metathesis-Active Ruthenium Alkylidene Complex	62
1.6.1.2	$(PCy_3)_2Cl_2Ru=CH-CH=CPh_2$, A Well-Defined Ruthenium Alkylidene Catalyst for the Metathesis of Acyclic Olefins	63
1.6.1.3	Initial Applications of Olefin Metathesis Chemistry Catalyzed by $(PCy_3)_2Cl_2Ru=CH-CH=CPh_2$	64
1.6.2	More Accessible Ruthenium Alkylidene Sources	65
1.6.3	2 nd -Generation Grubbs Catalysts	68
1.6.3.1	N-Heterocyclic Carbene (NHC) Ligands	70

1.6.4	Multi-Component Ruthenium-Based Olefin Metathesis Catalyst Systems and Homogeneous Catalyst Precursors	73
1.6.5	Solid-Supported Ruthenium-Based Olefin Metathesis Catalysts	74
1.6.6	Conclusions	80
	References	81
1.7	Synthesis of Ruthenium Carbene Complexes	86
	<i>Warren R. Roper</i>	
1.7.1	Introduction	86
1.7.2	The First Ruthenium Carbene Complexes	86
1.7.3	Ruthenium Methylene Complexes	88
1.7.4	Ruthenium Dihalocarbene Complexes	92
	Acknowledgments	93
	References	93
1.8	Synthesis of Rhodium and Ruthenium Carbene Complexes with a 16-Electron Count	95
	<i>Helmut Werner and Justin Wolf</i>	
1.8.1	Introduction	95
1.8.2	Rhodium(I) Carbenes from Diazoalkanes	95
1.8.3	Ruthenium(II) Carbenes and Vinylidenes from Terminal Alkynes	98
1.8.4	Conclusions	108
	Acknowledgements	109
	References	109
1.9	Mechanism of Ruthenium-Catalyzed Olefin Metathesis Reactions	112
	<i>Melanie S. Sanford and Jennifer A. Love</i>	
1.9.1	Introduction	112
1.9.2	First-Generation Bis-Phosphine Catalyst Systems	112
1.9.2.1	General Mechanistic Considerations	112
1.9.2.2	Substituent Effects in Ruthenium-Catalyzed Olefin Metathesis	116
1.9.2.3	Thermal Decomposition of Ruthenium Catalysts	118
1.9.2.4	Decomposition in the Presence of Functional Groups	120
1.9.2.5	Mechanistic Considerations in Other First-Generation Ruthenium Metathesis Catalysts	120
1.9.3	Second-Generation Ruthenium Olefin Metathesis Catalysts	123
1.9.3.1	General Mechanistic Considerations	124
1.9.3.2	Substituent Effects in Ruthenium-Catalyzed Olefin Metathesis	125
1.9.3.3	Thermal Decomposition of Ruthenium Catalysts	127
1.9.3.4	Decomposition in the Presence of Functional Groups	127
1.9.3.5	Other Second-Generation Ruthenium Catalysts	128
1.9.4	Conclusions	129
	References	130

1.10	Intrinsic Reactivity of Ruthenium Carbenes	132
	<i>Christian Adlhart and Peter Chen</i>	
1.10.1	Introduction	132
1.10.2	Electrospray Ionization Mass Spectrometry (ESI MS) of Transition Metal Complexes	135
1.10.2.1	Electrospray Ionization	135
1.10.2.2	Tandem Mass Spectrometry	136
1.10.2.3	Reaction Conditions in the Collision Cell of the Tandem ESI MS	137
1.10.3	General Reactivity of Ruthenium Carbene Complexes in the Gas Phase	139
1.10.3.1	Dissociative Mechanism	139
1.10.3.2	Evidence for ROMP and RCM	141
1.10.3.3	Systematic Variation of a Common Structural Motif – Steric Effects and Halogen Effects	143
1.10.3.4	Conclusions	146
1.10.4	Three Key Factors that Determine the Activity of Metathesis Catalysts	147
1.10.4.1	Solution-Phase Pre-Equilibria: Activation	147
1.10.4.2	Pre-Equilibria During the Turnover: Backbiting	148
1.10.4.3	Catalyst Commitment: Potential Surface	155
1.10.5	Conclusions	167
	Compound Numbers	167
	References	169
1.11	The Discovery and Development of High Oxidation State Alkylidyne Complexes for Alkyne Metathesis	173
	<i>Richard R. Schrock</i>	
1.11.1	Introduction	173
1.11.2	Alkylidyne Complexes of Tantalum	174
1.11.3	Alkylidyne Complexes of Tungsten	174
1.11.4	Formation of Trialkoxy Alkylidyne Complexes from $W_2(OR)_6$ Species	178
1.11.5	Alkylidyne Complexes of Molybdenum	180
1.11.6	Reactions that Limit Metathesis Activity	181
1.11.7	Alkylidyne Complexes of Rhenium	185
1.11.8	Conclusions and Comments	186
	Acknowledgments	187
	References	187
1.12	Well-Defined Metallocarbenes and Metallocarbynes Supported on Oxide Supports Prepared via Surface Organometallic Chemistry: A Source of Highly Active Alkane, Alkene, and Alkyne Metathesis Catalysts	190
	<i>Christophe Copéret, Frédéric Lefebvre, and Jean-Marie Basset</i>	
1.12.1	Introduction	190
1.12.2	Preparation and Characterization of Well-Defined Metallocarbenes and Metallocarbynes via Surface Organometallic Chemistry	191

1.12.2.1	Strategy and Tools in Surface Organometallic Chemistry	191
1.12.2.2	Application to the Preparation of Well-Defined Metallocarbene and Metallocarbyne Supported on Oxides	192
1.12.3	Reactivity in Alkene and Alkyne Metathesis	195
1.12.3.1	Group 5 and 6 Metallocarbenes and Metallocarbynes Supported on Oxides	195
1.12.3.2	Group 7 Metallocarbenes and Metallocarbynes Supported on Oxides	197
1.12.4	Reactivity in Alkane Metathesis	200
1.12.5	Summary and Outlook	201
	Acknowledgments	202
	References	202

Index	205
--------------	-----

Volume 2

List of Contributors xxi

2.1	Olefin Metathesis and Related Reactions in Organic Synthesis: Introduction to Metal-Carbon Double Bonds in Organic Synthesis	1
	<i>Robert H. Grubbs</i>	
	References	4
2.2	General Ring-Closing Metathesis	5
	<i>So-Yeop Han and Sukbok Chang</i>	
2.2.1	Introduction	5
2.2.2	Synthesis of Carbocycles	7
2.2.2.1	Carbocyclization	7
2.2.2.2	Medium-Sized Carbocycles	16
2.2.2.3	Spiro Carbocycles	22
2.2.3	Synthesis of Bridged Bicycloalkenes	24
2.2.4	Synthesis of Heterocycles Containing Si, P, S, or B	29
2.2.4.1	Si-Heterocycles	29
2.2.4.2	P-Heterocycles	32
2.2.4.3	S-Heterocycles	35
2.2.4.4	B-Heterocycles	37
2.2.5	Synthesis of Cyclic Ethers	38
2.2.5.1	Mono- and Bicyclic Ethers	38
2.2.5.2	Polycyclic Ethers	43
2.2.6	Applications to N-Heterocycles and Peptide Chemistry	46
2.2.6.1	N-Heterocycles	46
2.2.6.2	Small and Medium-Sized Lactams	52
2.2.6.3	Cyclic Amino Acids, Peptides, and Peptidomimetics	54
2.2.7	Synthesis of Macrocycles	65
2.2.7.1	Macrocycles	66

2.2.7.2	Macrolactones	68
2.2.7.3	Macrolactams	73
2.2.8	Synthesis of Cyclic Conjugated Dienes	74
2.2.9	Alkyne Metathesis	77
2.2.10	Enyne Metathesis	80
2.2.10.1	General Enyne Metathesis	80
2.2.10.2	Dienyne Metathesis	83
2.2.11	Multi-Directional RCM	86
2.2.12	Tandem Processes	88
2.2.12.1	Tandem ROM/RCM	88
2.2.12.2	Other Tandem RCM	92
2.2.13	Asymmetric RCM	94
2.2.14	Synthesis of Complex Molecules	96
2.2.14.1	Template-Directed RCM	96
2.2.14.2	RCM in Supramolecular Chemistry	96
2.2.14.3	Synthetic Applications	109
	References	119
2.3	Catalytic Asymmetric Olefin Metathesis	128
	<i>Amir H. Hoveyda</i>	
2.3.1	Introduction	128
2.3.2	The Catalyst Construct	129
2.3.3	Mo-Catalyzed Kinetic Resolution With Hexafluoro-Mo Catalysts	129
2.3.4	Chiral Mo-Diolate Complexes for Kinetic Resolution and Asymmetric Synthesis	130
2.3.4.1	Chiral Biphen-Mo Catalysts	130
2.3.4.2	Catalytic Kinetic Resolution Through Mo-Catalyzed ARCM	130
2.3.4.3	Catalyst Modularity and Optimization of Mo-Catalyzed ARCM Efficiency and Selectivity	131
2.3.4.4	Catalytic Asymmetric Synthesis Through Mo-Catalyzed ARCM	133
2.3.4.5	Catalytic Asymmetric Synthesis Through Tandem Mo-Catalyzed AROM/RCM	137
2.3.4.6	Catalytic Asymmetric Synthesis Through Tandem Mo-Catalyzed AROM/CM	142
2.3.4.7	Towards User-Friendly and Practical Chiral Mo-Based Catalysts for Olefin Metathesis	143
2.3.5	Chiral Ru-Based Olefin Metathesis Catalysts	145
2.3.6	Conclusions and Outlook	147
	Acknowledgments	148
	References	148
2.4	Tandem Ring-Closing Metathesis	151
	<i>Stefan Randl and Siegfried Blechert</i>	
2.4.1	Introduction	151
2.4.2	Tandem Metathesis Involving Double Bonds Only	152
2.4.2.1	RRM of Alkenyl-Substituted Cycloolefins	152
2.4.2.2	RRM of <i>bis</i> Alkenyl-Substituted Cycloolefins	160

2.4.2.3	Tandem Reactions of Polycycloolefins	164
2.4.3	Tandem RCM Involving Enyne Reactions	164
2.4.3.1	Tandem Reactions with Triple Bonds As “Relays”	164
2.4.3.2	Tandem Processes Involving Ring Rearrangement	166
2.4.3.3	Alkyne Trimerizations Catalyzed by Metathesis Catalysts	169
2.4.3.4	Other Tandem Processes Involving C–C Triple Bonds	171
2.4.4	Summary and Outlook	172
	References	173
2.5	Ene-Yne Metathesis	176
	<i>Miwako Mori</i>	
2.5.1	Introduction	176
2.5.2	Transition Metal-Carbene Complex-Catalyzed Enyne Metathesis	180
2.5.2.1	Ring-Closing Metathesis (RCM) of Enyne Using Ruthenium Carbene Complex	180
2.5.2.2	Ring-Opening Metathesis–Ring-Closing Metathesis of Cycloalkene-Yne	186
2.5.2.3	Intermolecular Enyne Metathesis (Cross-Metathesis)	188
2.5.3	Skeletal Reorganization Using Transition Metals	194
2.5.4	Utilization of Enyne Metathesis for the Synthesis of Natural Products and Related Biologically Active Substances	198
2.5.5	Perspective	200
	References	203
2.6	Ring-Opening Cross-Metatheses	205
	<i>Thomas O. Schrader and Marc L. Snapper</i>	
2.6.1	Introduction	205
2.6.2	Early Examples of ROCM	206
2.6.2.1	Mechanistic Insight	206
2.6.2.2	Early Efforts toward a Selective ROCM	207
2.6.2.3	Well-Defined Metal Complexes as Catalysts	209
2.6.2.4	New Opportunities for Olefin Metathesis	212
2.6.3	Selective ROCM Reactions	213
2.6.3.1	ROCM Involving Cyclobutenes	213
2.6.3.2	Regio- and Stereoselective ROCM	216
2.6.3.3	ROCM of Bridged Bicyclic Alkenes	218
2.6.3.4	ROCM Reactions of Cyclopropenes	223
2.6.3.5	ROCM Reactions Involving Unstrained Cycloolefins	224
2.6.3.6	ROCM Reactions of Trisubstituted Olefins	224
2.6.3.7	Variations of ROCM	226
2.6.3.8	Ring Expansion via Olefin Metathesis	226
2.6.4	Enantioselective ROCM	228
2.6.4.1	Mo-Catalyzed Asymmetric ROCM	228
2.6.4.2	A Recyclable Chiral Ruthenium Catalyst for Asymmetric ROCM	230
2.6.5	ROCM in Total Synthesis	230
2.6.6	Conclusions	233
	References	235

2.7	Ring-Expansion Metathesis Reactions	238
	<i>Choon Woo Lee</i>	
	References	244
2.8	Olefin Cross-Metathesis	246
	<i>Arnab K. Chatterjee</i>	
2.8.1	Olefin Forming Cross-Coupling Reactions	246
2.8.2	Olefin Metathesis and Selectivity Problems in CM	247
2.8.3	Metathesis Catalyst Overview	249
2.8.4	Selectivity Challenges in CM	250
2.8.5	Stereoselective CM Reactions	252
2.8.6	Product-Selective Reactions by CM	256
2.8.7	Styrene CM Reactions	258
2.8.8	Trisubstituted Olefin Synthesis by CM	261
2.8.9	Electron-Poor Olefins in CM	264
2.8.10	Reagent Synthesis by CM	269
2.8.11	Applications of CM	275
2.8.12	Bioorganic Applications of CM	278
2.8.13	CM Product-Selectivity Model	288
2.8.14	Conclusions	290
	References	292
2.9	Olefin Metathesis Strategies in the Synthesis of Biologically Relevant Molecules	296
	<i>Jennifer A. Love</i>	
2.9.1	Introduction	296
2.9.1.1	Olefin Metathesis Strategies in Complex Molecule Synthesis	296
2.9.1.2	Catalysts for Olefin Metathesis	297
2.9.2	RCM and ROM in Complex Molecule Synthesis	298
2.9.2.1	Laulimalide	298
2.9.2.2	Boronolide	302
2.9.2.3	Ingenol	303
2.9.2.4	Asteriscanolide	303
2.9.2.5	(+)-FR900482	305
2.9.2.6	Salicylihalamide	306
2.9.2.7	Roseophilin	307
2.9.2.8	Ircinal A and Manzamine A	309
2.9.2.9	Amphidinolide A	309
2.9.2.10	Peptidomimetics	310
2.9.3	Ring-Closing Ene-Yne Metathesis	312
2.9.4	Cross-Metathesis in the Synthesis of Complex Molecules	314
2.9.4.1	(-)-Cylindrocyclophanes A and F	314
2.9.4.2	Garsubellin A	315
2.9.4.3	(+)-Brefeldin A	315

2.9.5	ROMP in Complex Molecule Synthesis	316
2.9.6	Conclusions	318
	References	319
2.9	Vignette 1	
	The Olefin Metathesis Reaction in Complex Molecule Construction	323
	<i>K. C. Nicolaou and Scott A. Snyder</i>	
	Acknowledgments	334
	References	335
2.9	Vignette 2	
	Applications of Ring-Closing Metathesis to Alkaloid Synthesis	338
	<i>Stephen F. Martin</i>	
	Introduction	338
	Methodological Studies	339
	Synthesis of Alkaloid Natural Products	342
	Conclusions	350
	Acknowledgments	351
	References	351
2.9	Vignette 3	
	Radicalol and the Epothilones: Total Synthesis of Novel Anticancer Agents Using Ring-Closing Metathesis	353
	<i>Jon T. Njardarson, Robert M. Garbaccio, and Samuel J. Danishefsky</i>	
	References	359
2.10	The Use of Olefin Metathesis in Combinatorial Chemistry: Supported and Chromatography-Free Syntheses	361
	<i>Andrew M. Harned, Donald A. Probst, and Paul R. Hanson</i>	
2.10.1	Introduction	361
2.10.2	Metathesis Reactions Toward Supported Synthesis and Library Generation	362
2.10.2.1	Ring-Closing Metathesis (RCM)	362
2.10.2.2	Cross-Metathesis (X-MET)	369
2.10.3	Polymer-Supported Metathesis Catalysts	375
2.10.4	ROMP-Based Strategies	377
2.10.4.1	ROMPgels Reagents	378
2.10.4.2	ROMP as a Purification Tool	386
2.10.4.3	ROMPspheres	390
2.10.4.4	ROM Polymers as Supports	391
2.10.5	Conclusions	396
	Acknowledgements	399
	References	399

2.11	Metal-Catalyzed Olefin Metathesis in Metal Coordination Spheres	403
	<i>Eike B. Bauer and J. A. Gladysz</i>	
2.11.1	Introduction	403
2.11.2	Earliest Literature	404
2.11.3	Ferrocenes	405
2.11.4	Sophisticated Target Molecules: Catenanes and Knots	410
2.11.5	Systematic Investigation of Reaction Scope	414
2.11.6	Additional Literature Examples	420
2.11.7	Towards Additional Types of Sophisticated Target Molecules	425
2.11.8	Summary	429
2.11.9	Addendum	429
	Acknowledgments	429
	References	430
2.12	Alkyne Metathesis	432
	<i>Alois Fürstner</i>	
2.12.1	Introduction	432
2.12.2	Classical Catalyst Systems for Alkyne Metathesis	432
2.12.3	Recent Advances in Catalyst Design	434
2.12.4	Preparative Applications of Alkyne Metathesis	437
2.12.4.1	Alkyne Homometathesis Reactions	437
2.12.4.2	Alkyne Cross-Metathesis	439
2.12.4.3	Ring-Closing Alkyne Metathesis (RCAM)	443
2.12.4.4	Applications of RCAM to Natural Product Synthesis	448
2.12.4.5	Post-Metathesis Transformations Other Than Lindlar Hydrogenation: Selective Synthesis of (<i>E</i>)-Alkenes and Heterocyclic Motifs	456
2.12.5	Conclusions and Outlook	458
	References	459
2.13	Metathesis of Silicon-Containing Olefins	463
	<i>Bogdan Marciniak and Cezary Pietraszuk</i>	
2.13.1	Introduction	463
2.13.2	Self-Metathesis of Alkenylsilanes	464
2.13.3	Cross-Metathesis vs. Silylative Coupling (<i>Trans</i> -Silylation) of Alkenes with Vinylsilanes	464
2.13.4	Cross-Metathesis of Allylsilanes with Alkenes	470
2.13.5	Ring-Closing Metathesis of Silicon-Containing Dienes	472
2.13.6	Ring-Opening Metathesis/Cross-Metathesis	476
2.13.7	Polycondensation vs. Ring Closing of Divinyl-Substituted Silicon Compounds	478
2.13.8	ADMET Polymerization of Silicon-Containing Dienes	481
2.13.9	Ring-Opening Metathesis Polymerization of Silacycloalkenes	483
2.13.10	Ring-Opening Metathesis Polymerization of Silyl-Substituted Cycloalkenes	483
2.13.11	Degradation vs. Functionalization of Polymers	485
	References	486

2.14 Commercial Applications of Ruthenium Metathesis Processes 491*Richard L. Pederson*

- 2.14.1 Introduction 491
- 2.14.2 Fine Chemicals 491
 - 2.14.2.1 Agrochemicals: Insect Pheromones 492
 - 2.14.2.2 Polymer Additives 494
 - 2.14.2.3 Fuel Additives 494
 - 2.14.2.4 Drug Discovery 494
- 2.14.3 Pharmaceutical Applications 495
- 2.14.4 Future Directions for Metathesis 505
- 2.14.5 Summary 506
- References 507

Index 511**Volume 3****List of Contributors xxi****3.1 Introduction 1***Robert H. Grubbs***3.2 Living Ring-Opening Olefin Metathesis Polymerization 2***Gráinne Black, Declan Maher, and Wilhelm Risse*

- 3.2.1 Historic Overview of Living Polymerization Systems 2
- 3.2.2 Definition of Living Polymerization and Relevant Terminology 4
- 3.2.3 Introduction to ROMP 6
- 3.2.4 Olefin Metathesis Catalysts for Living Polymerizations 11
 - 3.2.4.1 Titanacyclobutane Compounds 11
 - 3.2.4.2 Tantalum-Alkylidene and Tantalacyclobutane Complexes for Norbornene Polymerizations 16
 - 3.2.4.3 Tungsten Catalysts 17
 - 3.2.4.4 Imido Molybdenum-Alkylidene Complexes 21
 - 3.2.4.5 Imido Tungsten- and Molybdenum-Alkylidene Catalysts for ROMP of Monomers Containing Cyclobutene, Bicyclooctadiene, and Bicyclooctatriene Ring Systems 33
 - 3.2.4.6 Tungsten- and Molybdenum-Alkylidene Catalysts in Cyclopentene Polymerizations 42
 - 3.2.4.7 Paracyclophene Polymerizations 43
 - 3.2.4.8 Ruthenium Catalysts and Living ROMP 44
 - 3.2.4.9 Star-Shaped Polymers via ROMP 63
 - References 66

3.3 Synthesis of Copolymers 72*Ezat Khosravi*

- 3.3.1 Introduction 72

3.3.2	Random Copolymers	72
3.3.3	Block Copolymers	76
3.3.3.1	Sequential Addition of Monomers	76
3.3.3.2	Coupling Reaction	83
3.3.3.3	Transformation of Propagating Species	84
3.3.3.4	Application of Well-Defined Bimetallic Initiators	90
3.3.4	Comb and Graft Copolymer	92
3.3.4.1	Combination of ROMP and Anionic Polymerization	92
3.3.4.2	Combination of ROMP and ATRP	94
3.3.4.3	Combination of ROMP and Cationic Polymerization	95
3.3.4.4	Combination of ROMP and Wittig-Type Reaction	96
3.3.4.5	Repetitive ROMP	96
3.3.5	Multi-Shaped Copolymers	98
3.3.6	Alternating Copolymers	103
3.3.7	Cross-Linked Copolymers	105
3.3.7.1	Well-Defined, Cross-Linked System via Direct Copolymerization	105
3.3.7.2	Cross-Linked Systems via Homopolymerization of Monomers with Cross-Linkable Side Chains	110
3.3.7.3	Cross-Linked Material via Combination of ROMP and Oxidative Polymerization	112
	References	113
3.4	Conjugated Polymers	118
	<i>W. James Feast</i>	
3.4.1	Introduction	118
3.4.2	Strategies for Applying ROMP in the Synthesis of Conjugated Polymers	121
3.4.3	Direct Routes from Monomer to Conjugated Polymer Via Chain-Growth Processes	122
3.4.4	Direct Routes from Monomer to Conjugated Polymer Via Step-Growth Processes	127
3.4.5	Indirect Routes to Conjugated Polymer Via Processable Precursor Polymers	129
3.4.6	Conclusions	139
	References	139
3.5	Stereochemistry of Ring-Opening Metathesis Polymerization	143
	<i>James G. Hamilton</i>	
3.5.1	Introduction	143
3.5.2	Consequences of <i>cis/trans</i> Isomerism and Tacticity in ROMP Polymers	144
3.5.3	Determination of the Stereochemistry of ROMP Polymers	146
3.5.3.1	<i>Cis/trans</i> Double-Bond Ratio	146
3.5.3.2	Tacticity	149
3.5.4	Control and Interpretation of Stereochemistry	156

3.5.4.1	Ratio and Distribution of <i>cis</i> and <i>trans</i> Double Bonds	156
3.5.4.2	Tacticity	169
	References	176
3.6	Syntheses and Applications of Bioactive Polymers Generated by Ring-Opening Metathesis Polymerization	180
	<i>Laura L. Kiessling and Robert M. Owen</i>	
3.6.1	Introduction	180
3.6.2	Synthesis of Biologically Active Polymeric Displays	183
3.6.2.1	Carbohydrate-Containing Polymeric Displays	183
3.6.2.2	Peptide-Substituted Polymers	189
3.6.2.3	Synthesis of DNA/Polymer Conjugates via ROMP	193
3.6.2.4	Synthesis of Drug/Polymer Conjugates via ROMP	195
3.6.2.5	Post-Polymerization Modification Strategies	196
3.6.2.6	End-Capping Strategies	199
3.6.3	Applications of Biologically Active Polymeric Displays	203
3.6.3.1	Protein-Carbohydrate Interactions	203
3.6.3.2	Integrins and Cellular Adhesion	211
3.6.3.3	Pathogenic Organisms	213
3.6.3.4	Cell Clustering	216
3.6.3.5	Bacterial Chemotaxis	216
3.6.4	Conclusions	220
	References	222
3.7	Metathesis Polymerization: A Versatile Tool for the Synthesis of Surface-Functionalized Supports and Monolithic Materials	226
	<i>Michael R. Buchmeiser</i>	
3.7.1	Introduction	226
3.7.2	Precipitation Polymerization-Based Techniques	226
3.7.3	Grafting Techniques	230
3.7.4	Coating Techniques	239
3.7.5	Monolithic Supports	240
3.7.5.1	Basics and Concepts	241
3.7.5.2	Manufacture of Metathesis-Based Monolithic Supports	242
3.7.5.3	Microstructure of Metathesis-Based Rigid Rods	242
3.7.5.4	Functionalization, Metal Removal, and Metal Content	245
3.7.5.5	Applications of Functionalized Metathesis-Based Monoliths in Catalysis	247
3.7.6	Conclusions, Summary, and Outlook	251
	Acknowledgments	251
	References	251
3.8	Telechelic Polymers from Olefin Metathesis Methodologies	255
	<i>Christopher W. Bielawski and Marc A. Hillmyer</i>	
3.8.1	Introduction and Background	255

3.8.2	Telechelic Polymers from Metathesis Polymerizations	258
3.8.2.1	Molecular Weight and Functionality Control in a ROMP/CT System	260
3.8.3	Syntheses and Applications of Telechelic Polymers Prepared Using Metathesis	263
3.8.3.1	Synthesis of Telechelic Polymers Using Ill-Defined Catalysts	264
3.8.3.2	Synthesis of Telechelic Polymers Using Well-Defined Metal Alkylidenes	267
3.8.3.3	Synthesis of End-Functionalized Polymers Using Functionalized Initiators	277
3.8.4	Conclusions and Outlook	279
	References	280
3.9	ADMET Polymerization	283
	<i>Stephen E. Lehman, Jr. and Kenneth B. Wagener</i>	
3.9.1	Introduction	283
3.9.2	ADMET: The Metathesis Polycondensation Reaction	288
3.9.2.1	Kinetics and Equilibrium Considerations	289
3.9.2.2	Molecular Weight Distribution	291
3.9.2.3	Interchange Reactions	291
3.9.2.4	Cyclization vs. Polymerization	292
3.9.2.5	Monomer Purity	293
3.9.3	Early Observations in the Evolution of ADMET Polymerization: Reactions of Non-Conjugated Dienes with Classical Metathesis Catalysts	294
3.9.4	ADMET of Non-Conjugated Hydrocarbon Dienes with Well-Defined Metathesis Catalysts	297
3.9.4.1	Linear Terminal Dienes	297
3.9.4.2	Branched Terminal Dienes	300
3.9.4.3	Geminal Disubstituted Olefins	305
3.9.4.4	1,2-Disubstituted Olefins	307
3.9.4.5	Trisubstituted Olefins	308
3.9.5	ADMET Copolymerization	310
3.9.6	Synthesis of Conjugated Polymers via ADMET	311
3.9.6.1	Polyacetylenes	311
3.9.6.2	Polyphenylenevinylenes	313
3.9.6.3	Other Conjugated Polymers	315
3.9.7	ADMET Polymerization of Functionalized Dienes	316
3.9.7.1	Ethers, Acetals, and Alcohols	318
3.9.7.2	Amines	319
3.9.7.3	Boronates	320
3.9.7.4	Thioethers	321
3.9.7.5	Carbonyl Compounds	322
3.9.7.6	Halides	325
3.9.7.7	Silicon Compounds	325

3.9.7.8	Organometallic Compounds	329
3.9.8	Retro-ADMET: Towards Recycling of Unsaturated Polymers with Well-Defined Metathesis Catalysts	329
3.9.9	Telechelic Oligomers via ADMET	331
3.9.10	Kinetics and Mechanism	332
3.9.11	Modeling Polyolefins with ADMET	338
3.9.11.1	Hydrogenation of ADMET Polymers	338
3.9.11.2	Branched Polyethylene	339
3.9.11.3	Functionalized Polyethylene	342
3.9.12	Towards Biologically Useful Polymers via ADMET	345
3.9.13	Solid-State Polymerization	347
3.9.14	Conclusions and Outlook	347
	References	347
3.10	Acyclic Diyne Metathesis Utilizing <i>in Situ</i> Transition Metal Catalysts: An Efficient Access to Alkyne-Bridged Polymers	354
	<i>Uwe H. F. Bunz</i>	
3.10.1	Introduction	354
3.10.1.1	Alkyne Metathesis	355
3.10.2	ADIMET: Synthesis of Alkyne-Bridged Polymers	357
3.10.2.1	Synthesis of PPEs by <i>in situ</i> ADIMET	360
3.10.2.2	Synthesis of PPE-PPV Copolymers by <i>in situ</i> ADIMET	363
3.10.2.3	Synthesis of Other PAEs by ADIMET	365
3.10.2.4	Alkyne-Bridged Carbazole Polymers (PCE) by ADIMET	370
3.10.3	Conclusions	370
	Acknowledgments	371
	References	371
3.11	Polymerization of Substituted Acetylenes	375
	<i>Toshio Masuda and Fumio Sanda</i>	
3.11.1	Introduction	375
3.11.2	Polymerization Catalysts	378
3.11.2.1	Mo and W Catalysts	378
3.11.2.2	Nb and Ta Catalysts	381
3.11.2.3	Rh Catalysts	382
3.11.2.4	Other Group 8–10 Metal Catalysts	384
3.11.3	Controlled Polymerizations	384
3.11.3.1	Living Polymerization by Metal Halide-Based Metathesis Catalysts	385
3.11.3.2	Living Polymerization by Single-Component Metal-Carbene Catalysts	387
3.11.3.3	Stereospecific Living Polymerization by Rh Catalysts	388
3.11.4	New Monomers and Functional Polymers	389
3.11.4.1	Gas-Permeable Polyacetylenes	396
3.11.4.2	Optically Active Polyacetylenes	397

3.11.4.3	Other Functional Polyacetylenes	399
	References	401

3.12 Commercial Applications of Ruthenium Olefin Metathesis Catalysts in Polymer Synthesis 407

Mark S. Trimmer

3.12.1	Introduction	407
3.12.2	Background	407
3.12.3	New Developments	408
3.12.4	Poly-DCPD	409
3.12.5	Other ROMP Polymers	411
3.12.6	Hydrogenated ROMP Polymers	413
3.12.7	Depolymerization	414
3.12.8	Summary	414
	References	414

Index	419
--------------	------------

Preface

Robert H. Grubbs

Not only did Ziegler's discovery of metal-catalyzed olefin polymerizations forever change polymer science, but also the science surrounding it supplied the motivation for many areas of modern organometallic chemistry research [1]. Out of the explorations into new catalysts for the addition polymerization of olefins came a new type of catalyst, one that produced unsaturated polymers from cyclic olefins and ethylene-propylene copolymers from a simple propylene feed. It took a considerable amount of time, however, for researchers to realize that these two, apparently different, reactions were the same and that they represented a fundamentally new reaction.

While investigating the polymerization of norbornene with titanium-based reagents, researchers at Dupont were expecting to produce a Ziegler addition polymer. Instead, they obtained a highly unsaturated polymer in which the strained norbornene ring had been opened [2]. As other groups experimented with different cyclic olefins and other metal systems, these types of unsaturated polymers became generally available. Subsequently, in similar serendipitous fashion, while exploring the polymerization of propylene over molybdenum-based heterogeneous catalysts, an unexpected product was obtained. Rather than pure polypropylene, an ethylene-propylene copolymer had been formed. Analysis of the off-gases from the reaction revealed that butenes were produced as a byproduct. Based upon these findings, Eleuterio proposed a reaction in which the propylene was scrambled into two- and four-carbon fragments [3].

The Natta group's finding that cyclopentene could be ring-open polymerized demonstrated that highly strained olefins were not required for polymerization. Furthermore, the Italian group also broadened the range of catalysts capable of performing this transformation and found that the nature of the catalysts could control the stereochemistry of the resulting polymer. For example, when $\text{MoCl}_5/\text{Et}_3\text{Al}$ was employed as the catalyst, a polymer with a high *cis*-alkene content was produced. In contrast, however, the use of $\text{WCl}_6/\text{Et}_3\text{Al}$ resulted in the formation of a highly *trans* polymer [4]. Moreover, the discovery that the highly *trans* polymer obtained from cyclopentene was a potential substitute for natural rubber provided a focus for the development of olefin metathesis chemistry. The Calderon group at

Goodyear also developed a variety of new catalysts, and they were the first to recognize that the chemistry of both cyclic and acyclic olefins was, in fact, the same [5]. Subsequently, they developed homogeneous catalysts that would carry out the polymerization of cyclic olefins as well as the bond scrambling of acyclic olefins. Using appropriate labeling studies, this group also demonstrated that the reaction involved the cleavage and reformation of carbon-carbon double bonds, and not the exchange of alkyl groups. To account for the exchange reaction, the most straightforward mechanism consistent with this observation was proposed. In this formulation, the reaction would proceed through the pair-wise exchange of two olefins present in the coordination sphere of a metal complex through a “quasi-cyclobutane complex” [6]. This simple mechanism, however, was difficult to reconcile with observations that were subsequently made by Chauvin. In his studies of the cross-metathesis reactions of cyclopentene with acyclic olefins, he found that the ends of the acyclic olefin became disconnected during the reaction, resulting in a statistical mixture of kinetic products. In contrast, a pair-wise mechanism, such as the quasi-cyclobutane mechanism, would give rise to a non-statistical product ratio [7]. Initially, it was possible to rationalize the Chauvin results by adding complexity to the pair-wise mechanism. A variety of other mechanistic studies, however, demonstrated that the ends of an olefin did not exchange in a pair-wise fashion [8]. The Chauvin mechanism, therefore, was the most consistent with these results. Metal-carbene complexes were the smallest fragments that allowed the olefins to exchange one carbon atom at a time and, therefore, became the best candidates for use as catalysts for the reaction. The only carbene complexes known at that time were those prepared initially by the Fischer group. Studies of these complexes provided a model for the metathesis reaction, giving rise to suggestions of more defined metathesis mechanisms [9]. The chapter by Katz (Chapter 1.5) will discuss these developments.

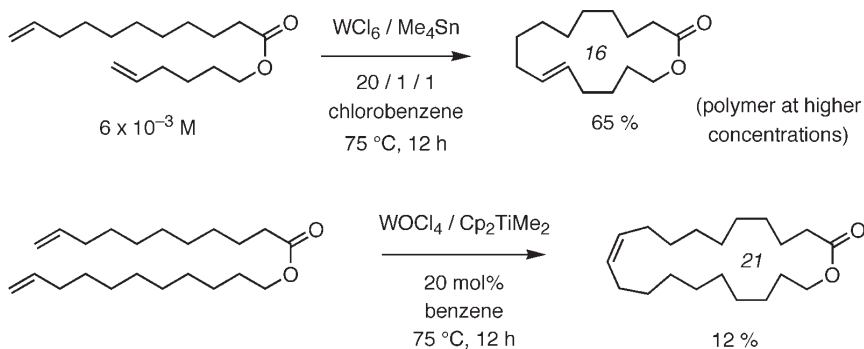
Higher oxidation state alkylidene (carbene) complexes provided strong support for this mechanism. The Tebbe complex was shown to be a catalyst for the exchange of terminal olefins, and the initiating and propagating carbenes could both be observed [10]. Moreover, when the reaction was carried out in the presence of a base, the intermediate metallacycle could be isolated. Not only did these metallacycles act as catalysts for olefin metathesis, but they were also found to be initiators for the living polymerization of norbornenes (Chapter 3.2). Furthermore, the intermediate carbene species could be trapped with phosphines. The groups of Schrock (Chapter 1.3) and Osborn [11] isolated well-characterized tungsten-alkylidene complexes that would catalyze olefin metathesis reactions at rates comparable to those observed in reactions that had, up until that point, been performed with the ill-defined catalysts. Ivin and Osborn were able to observe both the metallacyclobutane and the propagating metal-carbene complex when $W(=CHCMe_3)(Br_2)(OCH_2CMe_3)_2/GaBr_3$ was employed as the catalyst [12]. Both of these species could be observed by 1H NMR spectroscopy. In the more active catalysts that have been developed since these early observations, the alkylidene (carbene) intermediate is the major chain-carrying species. These early studies pro-

vided a strong support for the proposed mechanism and created the foundations upon which future developments were based.

Key to the recent explosion in the applications of olefin metathesis has been the evolution of highly active, single-site catalysts that are tolerant of most organic functional groups and can be used without complex experimental requirements. The evolution of these catalysts, and the surrounding organometallic chemistry, is covered in the first section of this handbook.

In parallel developments, applications of the metathesis reaction in the synthesis of non-polymeric molecules were also being explored. Since the early catalysts were poisoned by most functional groups, the initial focus fell upon simple hydrocarbon olefins. The foremost process was the SHOP process, producing olefins that were used in the synthesis of detergent alcohols. In fact, an array of specialty olefins was offered for a short time by Shell as an outgrowth of the SHOP process.

Significant observations regarding the application of olefin metathesis in the synthesis of more complex molecules were made by Villemin [13] and Tsuji [14] in 1980. Independently, they discovered that diolefins could be cyclized to form macrocyclic systems.



An important observation from the Tsuji paper was as follows: “In order to exploit the metathesis reaction as a truly useful synthetic methodology, it is essential to discover a new catalyst system which can tolerate the presence of functional groups in olefin molecules.” It was, initially, the well-defined molybdenum catalysts that provided the functional group tolerance that allowed metathesis to begin playing a role in the organic synthesis of highly functionalized compounds [15]. These developments were rapidly accelerated by the discovery of the family of ruthenium catalysts that were even more functional-group-tolerant than earlier metal complexes [16] and that could be used with standard organic methods instead of the “organometallic” techniques required with the molybdenum systems. As will be seen in the section on organic applications (Volume 2), an amazing array of new structures and methodologies has been developed in a rather short period of time.

Similarly, these catalyst developments have also led to the synthesis of a wide variety of new polymeric structures. The early finding that the use of well-defined titanium catalysts led to living polymerizations has been found to be general with other well-defined catalysts (initiators) utilized in ROMP polymerizations. An astonishing number of new polymeric structures have been prepared using these new catalysts, which have found applications in diverse areas ranging from biomolecular studies to the manufacture of baseball bats. The needs of polymer synthesis have driven much of the catalyst development and, in turn, applications of the catalyst. Unusually, this area is one in which reactions developed for polymer synthesis have had an impact on organic synthesis. Normally, technology flows in the opposite direction.

This handbook is divided into three sections based on the three parallel areas that have been developed by chemists with backgrounds in different areas. The catalysts have been the contribution of the organometallic chemists. This group provided the basic mechanistic details and synthetic techniques that were required to reach the present state of development. Polymer chemists have led the development of materials based on ROMP protocols, and applications in this area drove, in a synergistic fashion, much of the early catalyst development. The organic chemists have provided the examples that are elevating the metathesis reaction to a major tool for the construction of carbon-carbon bonds in small, and sometimes not so small, molecules. This area is now leading to new members of the family of catalysts, in an effort to meet the special requirements of stereochemistry and selectivity imposed by the synthesis of complex organic structures.

Chapter topics were chosen to provide broad coverage for all the areas of metathesis. There are two types of chapters in this handbook. Most are comprehensive and provide a compilation of the important developments within that specific area. Other shorter chapters have been contributed by some of the pioneers in the area, who provided background work that was essential for the present developments or were early users of the technology and demonstrated the potential applications.

Key to all of the applications is the availability of catalysts. In the first volume, the development of the many types of catalysts is covered, providing a background for the applications in the remainder of the handbook. A number of the pioneers, who developed many of the background reactions that have led to the present state of metathesis, have written short vignettes that provide a personal account of their contributions. Longer chapters have been written to provide comprehensive coverage of the fields of development.

In the remaining two sections, the applications of the olefin metathesis reaction in organic and polymer synthesis are described. It is becoming apparent that the present families of catalysts are allowing the early promise of olefin metathesis to be realized.

I wish to thank all of the authors for their diligent work in preparing their chapters in a timely manner and for their cooperation in dealing with last-minute changes. In addition, I wish to acknowledge the work of two of my coworkers, J. P. Morgan and Stuart J. Cantrill, who have helped with significant editing of some of the chapters.

References

- 1 ZIEGLER, K.; HOLZKAMP, E.; BREIL, H.; MARTIN, H. *Angew. Chem., Int. Ed.* **1955**, 67, 541.
- 2 TRUETT, W. L.; JOHNSON, D. R.; ROBINSON, I. M.; MONTAGUE, B. A. *J. Am. Chem. Soc.* **1960**, 82, 2337.
- 3 ELFUTERIO, H. S. US Pat. 3,074,918 and *J. Mol. Catal.* **1991**, 65, 55.
- 4 NATTA, G.; DALL'ASTA, G.; MAZZANTI, G.; PASSQUON, J. *Polymer Sci., Polymer Lett.* **1964**, B2, 349.
- 5 CALDERON, N.; OFSTEAD, E. A.; WARD, J. P.; JUDY, W. A.; SCOTT, K. W. *J. Am. Chem. Soc.* **1968**, 90, 4133.
- 6 CALDERON, N.; CHEN, H. Y.; SCOTT, K. W. *Tetrahedron Lett.* **1967**, 3327.
- 7 HERISSON, J.-L.; CHAUVIN, Y. *Makromol. Chem.* **1971**, 141, 161.
- 8 (a) GRUBBS, R. H.; BURK, P. L.; CARR, D. D. *J. Am. Chem. Soc.* **1975**, 97, 3265.
(b) KATZ, T. J.; ROTHCHILD, R. *J. Am. Chem. Soc.* **1976**, 98, 2519.
- 9 KATZ, T. J.; ACTON, N. *Tetrahedron Lett.* **1976**, 4251.
- 10 TEBBE, F. N.; PARSHALL, G. W.; REDDY, G. J. *Am. Chem. Soc.* **1978**, 100, 3611.
- 11 KRESS, H.; RUSSELL, M. J. M.; WESOLEK, M. G.; OSBORN, J. A. *J. Chem. Soc., Chem. Commun.* **1980**, 431.
- 12 KRESS, J.; OSBORN, H. A.; GREENE, R. M. E.; IVIN, K. H.; ROONEY, J. J. *J. Am. Chem. Soc.* **1987**, 109, 899.
- 13 VILLEMIN, D. *Tetrahedron Lett.* **1980**, 21, 1715.
- 14 TSUJI, J.; HASHIGUCHI, S. *Tetrahedron Lett.* **1980**, 21, 2955.
- 15 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, 114, 5426.
- 16 FU, G. C.; NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, 115, 9856.

List of Contributors

Prof. Dr. Jean-Marie Basset

Directeur de Recherche (DRCE)
Laboratoire de Chimie Organometallique de
Surface
UMR 9986 CNRS – CPE Lyon
Bat. 308, 43 Bd du 11 Novembre 1918
F-69616 Villeurbanne
France

Dr. Christopher W. Bielauski

Division of Chemistry and Chemical
Engineering
California Institute of Technology
Pasadena, CA 91129
USA

Professor Siegfried Blechert

Institut für Organische Chemie
Technische Universität Berlin
Str. D. 17 Juni 135
D-10623 Berlin
Germany

Prof. Dr. Michael R. Buchmeiser

Institute of Analytical Chemistry and
Radiochemistry
University of Innsbruck
Christoph-Probst-Platz
Innrain 52
6020 Innsbruck
Austria

Professor Uwe H. F. Bunz

Department of Chemistry and Biochemistry
The University of South Carolina
631 Sumter Street
Columbia, SC 29208
USA

Professor Sukbok Chang

Department of Chemistry
Ewha Womans University
Seoul 120-750
Korea

Dr. Arnab K. Chatterjee

Novartis Genomics Institute
Room C226
10675 John Hopkins Drive
San Diego, CA 92130
USA

Professor Dr. Peter Chen

Laboratory of Organic Chemistry
ETH Hoenggerberg, HCl
CH-8093, Zuerich
Switzerland

Professor Samuel J. Danishefsky

Department of Chemistry
Columbia University
Havemeyer Hall, MC 3106
3000 Broadway
New York, NY 10027
USA

Professor W. James Feast F. R. S.

Department of Chemistry
University of Durham
Durham DH1 3LE
UK

Professor Alois Fürstner

Direktor am Institut
Max Planck Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr
Germany

Dr. Mike Giardello

Materia
2531 Nina Street
Pasadena, CA 91107
USA

Professor John A. Gladysz

Insitut fur Organische Chemie
Universität Erlangen-Nürnberg
Henkestr. 42
91054 Erlangen
Germany

Dr. James G. Hamilton

The School of Chemistry
The Queens University of Belfast
Stranmillis Road
Belfast BT9 5AG
Northern Ireland

Professor Paul R. Hanson

Department of Chemistry
1251 Wescoe Hall Drive
1023 Malott Hall
The University of Kansas
Lawrence, Kansas 66045-7582
USA

Professor Marc Hillmyer

Department of Chemistry
University of Minnesota
207 Pleasant St. SE
Minneapolis, MN 55455-0431
USA

Professor Amir H. Hoveyda

Department of Chemistry, Merkert Center
Boston College
Chestnut Hill, MA 02467
USA

Professor Thomas J. Katz

Department of Chemistry
Columbia University
3000 Broadway, MC 3167
New York, New York 10027
USA

Dr. Ezat Khosravi

Department of Chemistry
University of Durham
Durham DH1 3LE
UK

Professor Laura L. Kiessling

Department of Chemistry and Biochemistry
University of Wisconsin, Madison
1101 University Ave
Madison, WI 53706
USA

Dr. Choon Woo Lee

Materia
2531 Nina Street
Pasadena, CA 91107
USA

Dr. Jennifer Love

Department of Chemistry and Chemical
Engineering
MC: 164-30
California Institute of Technology
Pasadena, CA 91125
USA

Professor Bogdan Marciniak

Organometallic Chemistry and Molecular
Catalysis
Adam Mickiewicz University
Coll. Chemicum
Grunwaldzka 6
60-780 Poznan POLAND

Professor Stephen F. Martin

Organic and Biochemistry Divisions
The University of Texas at Austin
Austin, TX 78712-1167
USA

Professor Toshio Masuda

Department of Polymer Chemistry
Faculty of Engineering
Kyoto University
Kyoto 606-8501
JAPAN

Professor Miwako Mori

Faculty of Pharmaceutical Sciences
Hokkaido University
Sapporo 060-0812
JAPAN

Professor Sonbinh T. Nguyen

Department of Chemistry
Northwestern University
2145 Sheridan Road
Evanston IL 60208
USA

Professor Kyriacos C. Nicolaou
 Department of Chemistry
 The Scripps Research Institute
 1550 N. Torrey Pines Road
 La Jolla, CA 92037
 USA

Dr. Richard L. Pedersen
 Materia
 2531 Nina Street
 Pasadena, CA 91107
 USA

Professor Wilhelm Risse
 Chemistry Department
 University College Dublin
 Belfield, Dublin 4
 Ireland

Professor Warren Roper
 Room 4051
 Faculty of Science
 Chemistry Department
 Private Bag: 92019
 23 Symonds Street
 The University of Auckland
 Auckland
 New Zealand

Dr. Melanie Sanford
 Department of Chemistry
 Princeton University
 121 Frick Laboratory
 Washington Road and William Street
 Princeton, NJ 08544-1009
 USA

Professor Richard R. Schrock
 Department of Chemistry
 Massachusetts Institute of Technology
 77 Massachusetts Ave, 18-390
 Cambridge, MA 02139-4307
 USA

Professor Marc L. Snapper
 Department of Chemistry
 Boston College
 Eugene F. Merkert Chemistry Center
 2609 Beacon Street
 Chestnut Hill, MA 02467
 USA

Dr. Mark S. Trimmer
 Materia
 2531 Nina Street
 Pasadena, CA 91107
 USA

Tina Trnka
 Division of Chemistry and Chemical
 Engineering
 California Institute of Technology
 Pasadena, CA 91125
 USA

Professor Kenneth B. Wagener
 Department of Chemistry
 University of Florida
 P.O. Box 117200
 4000 Central Florida Blvd
 Gainesville, FL 32611-7200
 USA

Professor Dr. H. C. Helmut Werner
 Institut für Anorganische Chemie
 Universität Würzburg
 Am Hubland
 D-97074 Würzburg
 Germany

1.1

Introduction

Robert H. Grubbs

The following section contains a detailed description of the development of the present families of catalysts. Historically, the first ill-defined or classical catalysts were derived from Ziegler catalyst systems and, therefore, were based on elements from the early transition metal series [1]. Although there were a few examples from the polymer field in which late metal catalysts were exploited for metathesis polymerizations, these candidates were initially ignored in the development of well-characterized systems. Calderon and his group [2], a major force in the early development of metathesis-based polymers, popularized the tungsten-derived systems, and, as a consequence, much of the early work was performed using these highly active catalysts. Most of the initial commercial applications – which employed soluble catalysts – were based on either tungsten or molybdenum systems. For example, the materials formed from dicyclopentadiene initially used tungsten hexachloride combined with alkyl aluminums to form a catalyst system in a reaction injection molding (RIM) process [3]. Later, molybdenum systems were also introduced for a similar process [4]. Furthermore, molybdenum-based heterogeneous catalysts have also served as the basis of the SHOP process [5] and the “Tri Olefin Processes” [6].

In a similar fashion, the first well-defined catalysts to emerge from organometallic chemistry were based on early metal complexes. Schrock introduced tantalum, tungsten, and molybdenum systems that became the basis (Chapter 1.3) for many of the early studies. In addition, the titanium-based “Tebbe” complex provided many of the early clues as to how the catalysts functioned (Chapter 1.2). Much of the history of these early developments is covered in the introductions to the chapters found in this section of the book. Although the most active classical catalysts were high oxidation state systems, the only metal-carbon double-bonded species known at the time of the proposal of the “carbene mechanism” were low oxidation state Fisher-type carbene complexes. Such compounds were examined as possible catalysts, and, although their activity was low, they played a vital role in the early development of this story, and a section is included on their reactions (Chapter 1.5).

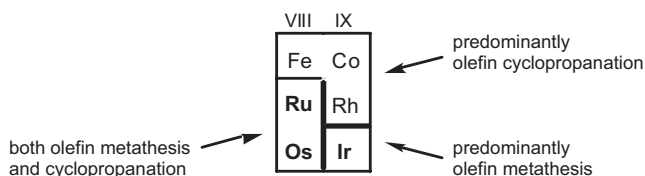
Ruthenium halide-based catalysts – for the polymerization of highly strained

olefins – were discovered in the mid-1960s. These catalysts were active only for the polymerization of strained olefins and generally involved long induction periods. Nevertheless, these systems were promising in that the reactions could be run with protic solvents and in the air. It was only with the synthesis of the first metathesis-active ruthenium-based complexes in 1992 that the full benefit of the increased environmental and functional group stability of these late metal complexes was finally realized. These applications will be amply demonstrated in the organic and polymer sections of these books.

The catalyst section of the handbook is organized around the metals upon which the complexes are based, thereby mirroring the way the field has developed. As new catalysts have been prepared that incorporate metals found later in the periodic table, the tolerance to functional groups has increased. In the following table, the standard functional groups are organized in increasing reactivity toward early metal catalysts. The relative reactivity of standard olefins is placed on this scale relative to the metal center. Until recently, the activity of the metal center was inversely related to the functional group tolerance. Many of the new ruthenium based catalysts, however, are as active in many cases as their early metal counterparts.

Titanium	Tungsten	Molybdenum	Ruthenium	
Acids	Acids	Acids	Olefins	
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids	
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water	
Ketones	Ketones	Olefins	Aldehydes	
Esters, Amides	Olefins	Ketones	Ketones	
Olefins	Esters, Amides	Esters, Amides	Esters, Amides	↑ Increasing Reactivity

Other late metals also form metal-carbon multiple bonds. To date, however, ruthenium appears to be the optimum metal. Metal-carbon double-bonded systems of iron, cobalt, and rhodium react to produce cyclopropanes in stoichiometric reactions [7]. Ruthenium and osmium both form active metal-carbon double-bonded complexes. Whereas lower coordination number complexes can be catalytic metathesis catalysts, high coordination number complexes can give stoichiometric cyclopropanations. Iridium tends to be a metathesis catalyst in ill-defined systems, and both osmium and iridium complexes are generally less active metathesis catalysts than the corresponding ruthenium analogues. Furthermore, since they are much more expensive, they have not been well studied.



The initial chapters of the catalyst section of the book have been designed to provide a historical development of the present generations of metathesis catalysts. A number of these chapters detail the experiences and views of the pioneers in the development of these contributing areas of organometallic chemistry. Later sections provide detailed mechanistic information that is required in order to develop the applications presented in other parts of the book.

References

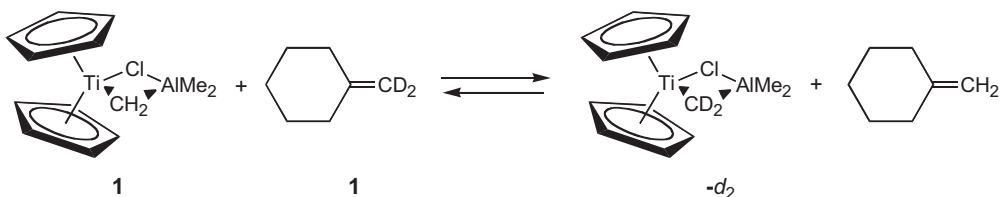
- 1 BANKS, R. L. *CHEMTECH* **1986**, 16, 112–117.
- 2 CALDERON, N.; OFSTEAD, E. A.; WARD, J. P.; JUDY, W. A.; SCOTT, D. W. *J. Am. Chem. Soc.* **1968**, 90, 4133–4140.
- 3 BRESLOW, D. S. *CHEMTECH* **1990**, 20, 540–544.
- 4 KIRKLAND, C. *Plastics World* **1990**, 50.
- 5 SHERWOOD, M. *Chem. Ind. (London)* **1982**, 994–995.
- 6 STRECK, R. *J. Mol. Catal.* **1992**, 76, 359–372.
- 7 BOYLE, M. P.; REN, T. *Prog. Inorg. Chem.* **2001**, 49, 113–168. SMITH, D. A.; REYNOLDS, D. N.; WOO, L. K. *J. Am. Chem. Soc.* **1993**, 115, 2511–2513. BROOKHART, M.; STUDABAKER, W. B. *Chem. Rev.* **1987**, 87, 411–432.

1.2

The Role of the “Tebbe Complex” in Olefin Metathesis

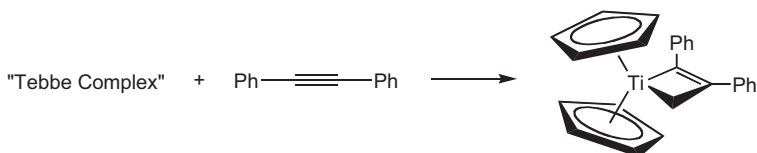
Robert H. Grubbs

Initial mechanistic studies of the olefin metathesis reaction suggested a pathway involving metal alkylidene and metallacycle complexes. Therefore, well-defined examples of such reactions were required to prove this conjecture. Early studies using Fischer carbene complexes demonstrated that these species could indeed promote metathesis; however, it was not possible to define the active intermediates in these systems [1]. In 1978, Fred Tebbe at DuPont reported the results of an investigation into the structure and reactivity of a compound – previously synthesized by Sinn and Kiminsky – that had been formulated as a titanium-methylene-aluminum complex. Tebbe was able to fully characterize the compound (1) and comment upon its reactivity [2]. Furthermore, in 1979, he reported that this complex was a catalyst for the degenerate metathesis of terminal olefins and was able to characterize the propagating methylene complex [3].



This reaction provided the first clean demonstration of the olefin metathesis reaction mechanism. A well-defined metal alkylidene had been shown to react with an olefin in a catalytic reaction to produce a well-defined propagating metal alkylidene (1- d_2).

Subsequently, it was demonstrated that reaction of these complexes with acetylenes resulted in the formation of metallacyclobutenes. In some cases, these metallacycles were formed reversibly and underwent acetylene exchange reactions [4].

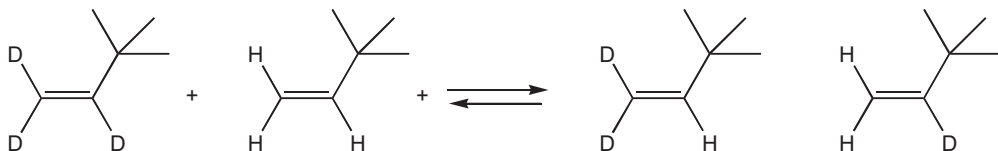


While examining this reaction – in an attempt to determine the stereochemistry of this well-defined reaction and to obtain some information about the structure of the proposed metallacycle intermediate – Tom Howard, in my laboratory at Caltech, isolated a stable metallacyclobutane complex [5]. A key factor in this reaction was the shifting of the equilibrium between the metallacycle and the aluminum adduct (the Tebbe complex) by using a strong base. Subsequently, dimethylamino-pyridine became the best base for the general synthesis of a variety of metallacycles.



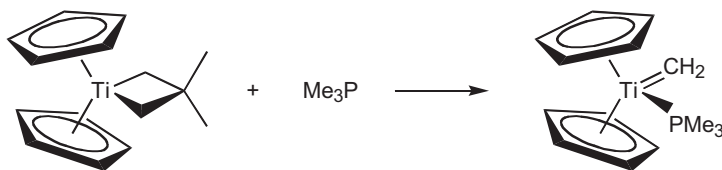
Consequently, a wide variety of metallacycles could be generated and became systems for the detailed study of the mechanism of a model metathesis reaction.

This metallacycle catalyzed the scrambling of the terminal groups of a pair of olefins, and the deuterium-labeled intermediate propagating metallacycles could also be observed.



The isolated metallacycles could be shown to undergo olefin exchange of the type required for the catalytic metathesis reaction. To complete the mechanistic study of the Tebbe complex-catalyzed reaction, the isolated metallacycle would react with dimethylaluminum chloride to regenerate the Tebbe complex.

In addition to trapping with aluminum halides, the intermediate methylene complex could be trapped by a variety of reagents, and it served as very clean starting materials for a variety of organometallic studies [6]. In agreement with the proposed metathesis mechanism, the metallacycles would react with trimethylphosphine to generate the phosphine methylene complex [7].



This series of isolated complexes served to identify all the intermediates in an operational olefin metathesis system. Although the Tebbe complex was a low-

activity catalyst, it provided an excellent model for the olefin metathesis reaction. The metallacycle complexes undergo very clean reactions and were perfect candidates for studying the mechanism of the metallacycle to carbene olefin interchange. Furthermore, very detailed studies were carried out to determine the role of the free titanium-methylene complex in the reaction [8]. The reaction of tungsten alkylidenes – in the polymerization of norbornenes – was examined by Ivan and Osborn, and, in one case, they were able to observe both the carbene and the metallacycle under the reaction conditions [9]. These observations provided excellent models for the intermediates in olefin metathesis catalyst systems.

Mechanistic studies employing appropriately labeled olefins, and using the classical, ill-defined catalyst systems, demonstrated only that in simple metathesis reactions, the kinetic products were also the thermodynamic products. This observation was inconsistent with the mechanism that was generally accepted at that time, which involved the exchange of the carbon atoms of a pair of olefins in the coordination sphere of a metal. The Chauvin metal-carbene to metallacyclobutane mechanism was the simplest explanation for the observations resulting from the labeling studies. Without the appropriate studies in which the intermediates were isolated and demonstrated to be kinetically competent, however, the general mechanism of metathesis remained in doubt. The results discussed above, combined with those provided in the early chapters by Schrock and Katz, confirmed the mechanistic proposals that had been suggested by labeling studies [10] of the ill-defined metathesis catalyst systems.

With the Tebbe complex at one extreme, it is now apparent that there is a range of catalysts in which the relative stabilities of the metal-carbene and the metallacycle vary. There are those species in which the metallacycle is the stable intermediate and others in which the metallacycle is too unstable to be observed. For example, the metallacycle has never been observed in the ruthenium catalysts (Chapter 1.6, 1.9, 1.10), and it has been proposed that, in these systems, the metallacycle may be in a transition state. As discussed by Schrock in Chapter 1.3, there have been a number of metallacycles and alkylidene complexes observed in the high oxidation state tungsten systems.

As will be discussed in the chapter on living polymerization, studies of the isolated metallacycles provided the first example of a living metathesis system [11]. It is now apparent that metathesis polymerizations, as mediated by most well-characterized complexes, are living. These living systems provide the control that has been essential for the development of ROMP as a major route for the synthesis of well-defined polymers.

References

- 1 Y. CHAUVIN, D. COMMEREUC, D. CRUPELINCK, *Makromol. Chem.* **1976**, 177, 2637.
- 2 F. N. TEBBE, G. W. PARSHALL, G. S. REDDY, *J. Am. Chem. Soc.* **1978**, 100, 3611–3613.
- 3 F. N. TEBBE, G. W. PARSHALL, D. W. OVENALL, *J. Am. Chem. Soc.* **1979**, 101, 5074–5075.
- 4 F. N. TEBBE, G. W. PARSHALL, D. W. OVENALL, *J. Am. Chem. Soc.* **1980**, 102, 6149–6151.

- 5 T. R. HOWARD, J. B. LEE, R. H. GRUBBS, *J. Am. Chem. Soc.* **1980**, *102*, 6876.
- 6 D. A. STRAUS, R. H. GRUBBS, *Organometallics* **1982**, *1*, 1658. J. B. LEE, K. C. OTT, R. H. GRUBBS, *J. Am. Chem. Soc.* **1982**, *104*, 7491.
- 7 J. D. MEINHART, E. V. ANSLYN, R. H. GRUBBS, *Organometallics* **1989**, *8*, 583–589.
- 8 E. V. ANSLYN, R. H. GRUBBS, *J. Am. Chem. Soc.* **1987**, *109*, 4880–4890. T. IKARIYA, S. C. H. HO, R. H. GRUBBS, *Organometallics* **1985**, *4*, 199. J. M. HAWKINS, R. H. GRUBBS, *J. Am. Chem. Soc.* **1988**, *110*, 2821–2823.
- 9 J. KRESS, J. A. OSBORN, K. J. IVIN, J. J. ROONEY, *J. Am. Chem. Soc.* **1987**, *109*, 899.
- 10 R. H. GRUBBS, C. HOPPIN, *J. Am. Chem. Soc.* **1979**, *101*, 1499 and references therein.
- 11 L. R. GILLIOM, R. H. GRUBBS, *J. Am. Chem. Soc.* **1986**, *108*, 733–742.

1.3

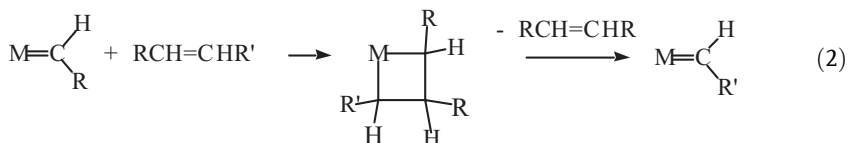
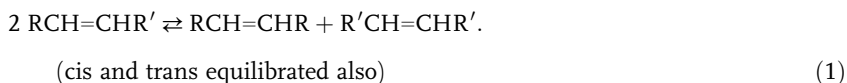
The Discovery and Development of High Oxidation State Mo and W Imido Alkylidene Complexes for Alkene Metathesis

Richard R. Schrock

1.3.1

Introduction

In the 1970s an intense interest in the catalytic olefin metathesis reaction began to develop [1]. In its simplest form the olefin metathesis reaction consists of a redistribution of alkylidene components of olefins (Eq. (1)). It was known to be promoted by tungsten, molybdenum, and rhenium, although at the time the reactions were “black boxes,” with nothing known about the mechanism or the detailed nature of the catalyst. Among the proposals was one (in 1971) by Hérrison and Chauvin that turned out to be correct [2]. The mechanism consists of a reaction between an alkylidene complex (or carbene complex, as it was called at that time) and an olefin to give a metallacyclobutane intermediate, from which an olefin is lost and a new alkylidene



complex formed, as shown in Eq. (2). (Addition of the olefin to the alkylidene so as to place the R' group on the β carbon atom would yield a degenerate version of the reaction.) However, none of the known carbene complexes at the time, the vast majority of which were compounds that contained a heteroatom-stabilized (usually O or N) carbene ligand [3], were found to react with olefins in a catalytic metathesis-like fashion.

In the early days of olefin metathesis with classical systems, several publications appeared in which the authors attempted to apply metathesis to organic chemistry. Although there was some success in this direction [1], organic reactions in general

were plagued by the sensitivity of the classical catalysts to air, moisture, and many functionalities (especially those that contain a relatively acidic proton); by side reactions; and by the relatively short lifetime of many of the catalysts. It became clear that active species were present in very low concentrations and that isolation or even identification of such apparently unstable species was unlikely to be successful. What was needed were identifiable, relatively stable compounds that would behave as long-lived catalysts, compounds whose reactivity possibly even could be tuned for the required task.

In this chapter, I trace the discovery and development of well-characterized “high oxidation state” alkylidene (carbene) complexes that will metathesize olefins. The alkylidene complexes will be primarily of the imido alkylidene type. Other types (cationic alkylidene species) were prepared by Osborn [4–8], who played a significant role in unraveling the puzzle surrounding how alkylidenes were generated from oxo complexes. Other important tungsten alkylidene catalysts that do not contain oxo or imido groups were developed later in the laboratories of Basset [9, 10]. Other chapters in this book cover developments in other areas, including titanium chemistry that was begun by Tebbe and was extensively developed by Grubbs. The reader also may refer to comprehensive reviews for a broader and more comprehensive treatment of high oxidation state alkylidene complexes. The first review of high oxidation state alkylidene complexes was published in 1986 [11]. A second review appeared in 1991 [12]. Various aspects of chemistry involving d^0 alkylidene complexes have been covered in other articles [13–17]. A comprehensive review of d^0 alkylidene (and alkylidyne) complexes in the last decade (1991 to 2001) has also appeared recently [18]. The development of ruthenium catalysts, in particular by Grubbs, has generated a good deal of interest from organic chemists, in large part because of the simplicity of the preparation of ruthenium catalysts and the fact that they are relatively tolerant of water, oxygen, and many functionalities compared to early transition metal catalysts. The development of ruthenium catalysts is also covered extensively in other contributions in this book. (Chapter 1.6).

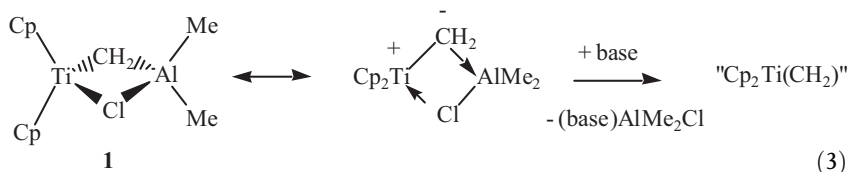
1.3.2

Tantalum Alkylidene Complexes

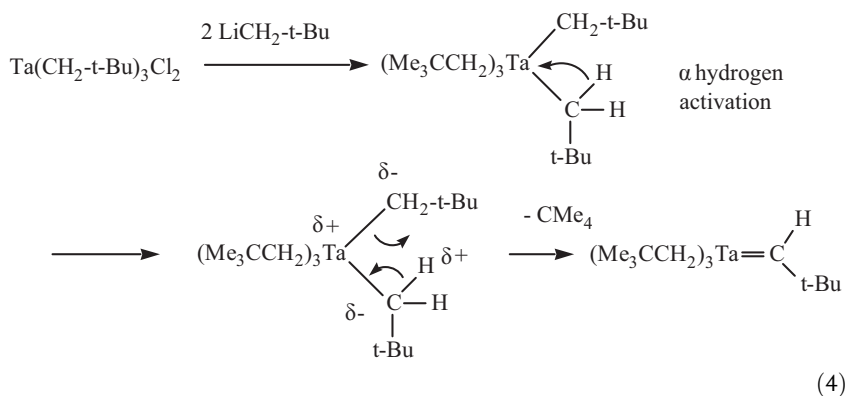
The development of alkylidene complexes that were stable enough to isolate and that were dramatically different from the Fischer-type carbene complexes that had been discovered in 1964 [3, 19] began in 1973 with studies involving tantalum alkyl complexes at the Central Research Department of E. I. duPont de Nemours and Company. The initial goal was simply to explore new chemistry of tantalum alkyl complexes.

At this time the chemistry of titanocene dialkyls was being explored by F. N. Tebbe. Tebbe discovered that the reaction between Cp_2TiCl_2 and excess $AlMe_3$ gave methane and **1** (Eq. (3)). (This work was not published until 1978 [20].) Although the methylene bridges between Ti and Al, later work suggested that **1** could serve

as a source of “ $\text{Cp}_2\text{Ti}(\text{CH}_2)$ ” in the presence of a base that would form an adduct with AlMe_2Cl [21]. It appeared that the $\text{Ti}-\text{CH}_2$ bond is polarized δ^+ on Ti and δ^- on C, exactly the opposite of a Fischer-type carbene complex, on the basis that the methylene ligand appears to be generated by “deprotonation” of a $\text{Ti}-\text{CH}_3$ species with an AlCH_3 species.



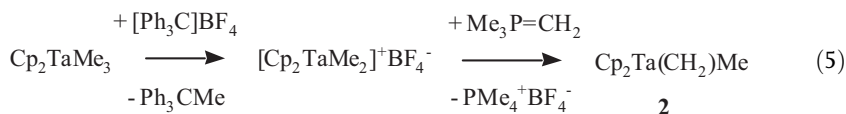
The only alkyl complexes of tantalum that existed in 1973 were methyl/chloride combinations containing a maximum of three methyl groups, e.g., TaMe_3Cl_2 [22]. The extensive work by Schmidbaur [23] on pentaalkyls and alkylidene trialkyls of phosphorus and arsenic and a report that same year of the synthesis of hexamethyltungsten [24] contributed to the decision to attempt to prepare pentamethyltantalum. The reaction between TaMe_3Cl_2 and two equivalents of LiMe indeed produced pentamethyltantalum [25], although it was found to melt above $\sim 0^\circ\text{C}$ and to decompose in a complex intermolecular fashion [26], which in retrospect is not unexpected, given the 10 electron count at the metal and the relatively sterically unprotected nature of a methyl group. Therefore, larger alkyls were employed in an attempt to prevent intermolecular decomposition. The reaction between TaR_3Cl_2 and two equivalents of LiR when $\text{R} = \text{CH}_2\text{Ph}$ gave red crystalline $\text{Ta}(\text{CH}_2\text{Ph})_5$, a species that was found to be much more stable than TaMe_5 [26]. When $\text{R} = \text{CH}_2\text{CMe}_3$, a similar reaction did not yield $\text{Ta}(\text{CH}_2\text{CMe}_3)_5$, but $(\text{Me}_3\text{CCH}_2)_3\text{Ta}=\text{CHCMe}_3$ (Eq. (4)), a “tantalum ylide” that bears an obvious relationship to a



phosphorus ylide, along with neopentane [27]. $(\text{Me}_3\text{CCH}_2)_3\text{Ta}=\text{CHCMe}_3$ is quite stable thermally, melting at $\sim 70^\circ\text{C}$ and distilling readily in a good vacuum. It is sensitive to oxygen, water, and a variety of functionalities, among them the organic carbonyl functionality, with which it reacts in a Wittig-like manner to yield poly-

meric $(\text{Me}_3\text{CCH}_2)_3\text{Ta}=\text{O}$ and the expected olefin [28]. All of these properties are reminiscent of phosphorus ylides [23] and further suggest that the alkylidene ligand is present in its closed shell dianionic configuration and that tantalum therefore is in the 5+ oxidation state. The principle of employing bulky, covalently bound ligands in order to stabilize pseudotetrahedral species against bimolecular decomposition, and the investigation of neopentyl complexes in particular, continued to be a central feature of the development of high oxidation state alkylidene chemistry and the development of alkene metathesis catalysts.

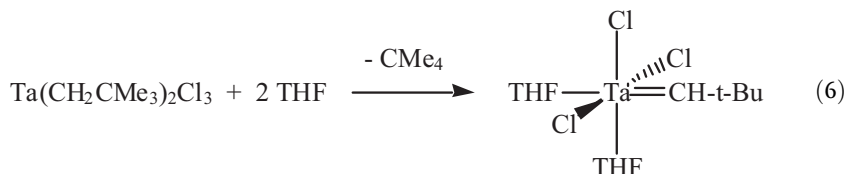
Efforts to stabilize tantalum methyl species by employing more bulky “ancillary” ligands led to the reaction between TaMe_3Cl_2 and two equivalents of TiCp to give Cp_2TaMe_3 [29]. Addition of trityl tetrafluoroborate to Cp_2TaMe_3 led to what could be called a “tantalonium” salt, as shown in Eq. (5). This cationic species was deprotonated by a phosphorus ylide to yield



the “tantalum ylide,” $\text{Cp}_2\text{Ta}(\text{CH}_2)\text{Me}$ [29]. Compound **2** was stable enough at room temperature to isolate and characterize completely; it was the first example of an isolable methylene complex. This species behaved as if the $\text{Ta}=\text{CH}_2$ bond were polarized $\delta+$ on Ta and $\delta-$ on the methylene carbon. For example, **2** would react with AlMe_3 to yield $\text{Cp}_2\text{TaMe}(\text{CH}_2\text{AlMe}_3)$. Compound **2**, an 18-electron species, was shown to decompose in a bimolecular fashion to yield an ethylene complex [30]. The fact that even an 18-electron methylene species will decompose in a bimolecular fashion, while 10-electron $\text{Ta}(\text{CHCMe}_3)(\text{CH}_2\text{CMe}_3)_3$ is quite stable thermally, was a dramatic indication that methylene complexes in general would be very much less stable than neopentylidene complexes. It was clear from X-ray studies [31] (and later from neutron diffraction studies [32]) that the tantalum-carbon bond was a full double bond, judging from the difference between the Ta–Me bond length (2.25 Å) and the $\text{Ta}=\text{CH}_2$ bond length (2.02 Å).

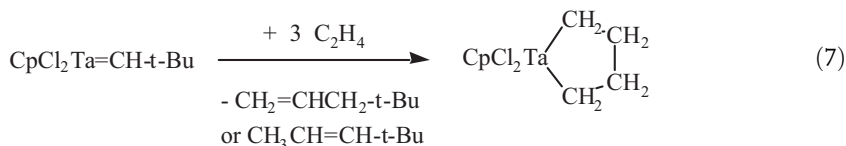
It soon became apparent that neopentyl ligands in d^0 complexes of Ta promote steric crowding and consequently are subject to a distortion that opens up the $\text{Ta}-\text{C}_\alpha-\text{C}_\beta$ angle and pushes the α hydrogens toward the metal. In a highly electrophilic metal complex such as hypothetical $\text{Ta}(\text{CH}_2\text{CMe}_3)_5$, which has a total of only 10 electrons in bonding and nonbonding metal-based orbitals, the electrons in a CH_α bond are thereby “activated” (as shown in Eq. (4)). As a consequence H_α becomes relatively acidic. (Interaction of a C–H electron pair with the metal later came to be called an α “agostic” interaction [33].) Migration of an α proton to a nearby nucleophilic neopentyl α carbon atom generates alkane and the $\text{Ta}=\text{C}$ bond. This proposed “ α hydrogen abstraction” can be viewed as essentially an intramolecular deprotonation reaction. However, metal-carbon bond homolysis followed by abstraction of an α hydrogen radical is a viable alternative. Homolysis tends to compete with α hydrogen abstraction when the metal-carbon bond and the

presumed agostic interaction are weaker, e.g., for niobium. Therefore, a “controlled” α hydrogen abstraction tends to be observed in an intramolecular fashion most often for d^0 complexes of Ta, Mo, W, and Re [11]. The methyl ligand is the least sterically protected and the least prone to be activated intramolecularly via an α agostic interaction. Therefore, the conditions that are required to induce α abstraction in a methyl complex often result in even more rapid decomposition of the methylene species that is formed. Observation of methylene species formed by an α abstraction reaction, which is often assisted by light, is rare [34]. Finally, α hydrogen abstraction can be induced by addition of a base. For example, $\text{Ta}(\text{CH}_2\text{CMe}_3)_2\text{Cl}_3$ is stable in pentane but rapidly turns purple in THF as 14-electron $\text{Ta}(\text{CHCMe}_3)(\text{THF})_2\text{Cl}_3$ (Eq. (6)) is formed quantitatively [35]. It is presumed that binding of THF to the tantalum center in $\text{Ta}(\text{CH}_2\text{CMe}_3)_2\text{Cl}_3$ leads to an increase in steric crowding and to subsequent acceleration of the α hydrogen abstraction reaction.



An important feature of high oxidation state alkylidene complexes that do not attain an 18-electron count about the metal was documented in a neutron diffraction study of $[\text{Ta}(\text{CH-t-Bu})\text{Cl}_3(\text{PMe}_3)]_2$ [36]. In this compound the Ta=C bond (1.90 Å) was found to be ~ 0.10 Å shorter than expected, the Ta=C–C angle to be 161° , and the Ta=C–H angle to be only 85° , i.e., the alkylidene is distorted by an α agostic interaction, one that is driven sterically to some extent by the bulk of the t-butyl group. Therefore, H_α could be said to be bonded to an orbital that has high p-character on carbon, as if C_α were essentially sp -hybridized. This is the reason that both J_{CH} (~ 90 Hz) and ν_{CH} (~ 2600 cm^{-1}) are unusually low in this and a variety of other electron-deficient d^0 alkylidene complexes of tantalum.

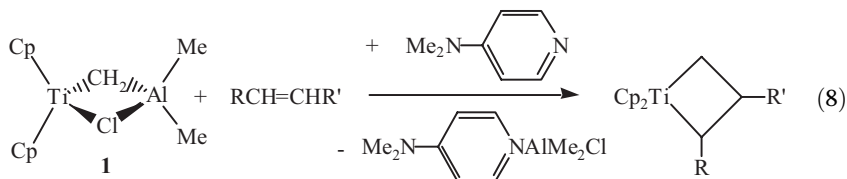
Isolation of electron-deficient, but stable, high oxidation state alkylidene species allowed their reactions with olefins to be explored in detail [37]. For example, $\text{TaCp}(\text{CH-t-Bu})\text{Cl}_2$ was found to react with terminal olefins to give products of rearrangement of an intermediate tantalacyclobutane complex, plus tantalacyclopentane complexes formed from the incipient tantalum(III) complex and two equivalents of olefin (e.g., as shown in Eq. (7)) [38]. A second



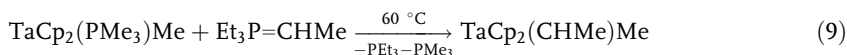
key observation was that while complexes such as $\text{Ta}(\text{CH-t-Bu})\text{Cl}_3(\text{PMe}_3)_2$ reacted with olefins similarly to yield products of rearrangement of unobservable interme-

diolate tantalacyclobutane complexes, complexes such as $\text{Ta}(\text{CH-t-Bu})\text{Cl}(\text{PMe}_3)(\text{O-t-Bu})_2$ led to productive metathesis of *cis*-2-pentene [39, 40]. This was the first time that productive metathesis of a simple olefin starting with a well-characterized carbene complex had been observed and was the first indication that alkoxide ligands encouraged metathesis versus metallacyclobutane rearrangement [16]. Unfortunately, the intermediate ethylidene and propylidene complexes could not be observed, apparently because those alkylidenes rearranged quickly to give ethylene and propylene, respectively. Presumably this is the reason (in part) that tantalum catalysts for the olefin metathesis reaction could not be prepared using various recipes that are successful for Mo or W [1].

Metallacyclobutane complexes of titanium began to appear in 1980 [12, 41–43]. (A titanacyclobutene complex was prepared from **1** and an alkyne in 1979 [44, 45].) Titanacyclobutanes could be prepared by removing the aluminum from **1** with a strong Lewis base in the presence of an olefin, as shown in Eq. (8). These metallacycles were stable with respect to rearrangement to an olefin via a β hydride process and showed a tendency to generate intermediate alkylidene complexes *in situ*. They ultimately proved to be useful as catalysts for the ring-opening metathesis polymerization of a variety of strained olefins [46, 47]. Complex **1** had been shown to be a catalyst for the nonproductive, degenerate metathesis of terminal olefins (methylene exchange) in 1979 [44].



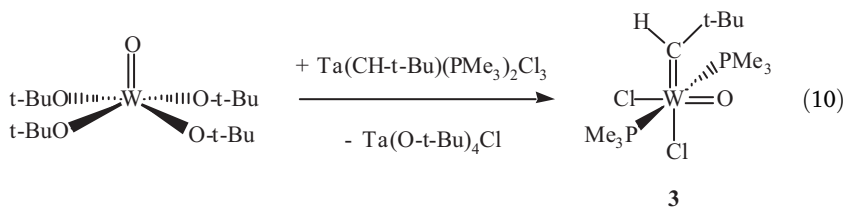
The reaction between $\text{TaCp}_2(\text{PMe}_3)\text{Me}$ and $\text{Et}_3\text{P=CHMe}$ was found to proceed as shown in Eq. (9) [48]. The fact that an alkylidene could be transferred from phosphorus to tantalum supported the proposal that the alkylidene was similar in each situation, i.e., a “nucleophilic” alkylidene.



1.3.3 Early Tungsten Alkylidene Complexes

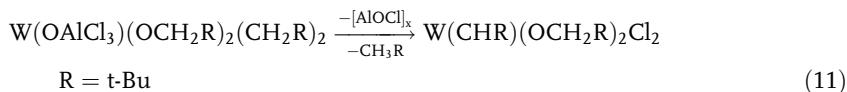
The two important findings to come out of tantalum chemistry, at least in terms of alkene metathesis, were that entirely new “high oxidation state” alkylidene complexes could be prepared and isolated and that alkoxides (relative to chlorides as ligands) appeared to “turn on” metathesis [39]. However, there was considerable doubt as to what combination of ligands would allow relatively stable, yet reactive, alkylidene complexes to be prepared, as well as metallacyclobutene complexes

that would lose an olefin to reform an alkylidene. Of particular concern was whether alkylidenes that contain one or more protons on the β carbon atom would be stable with respect to rearrangement of that alkylidene to an olefin. One compound that was thought to be a plausible target (before the importance of a sterically crowded pseudotetrahedral coordination sphere was appreciated) was $(\text{Me}_3\text{CO})_4\text{W}=\text{CHCMe}_3$. The reaction shown in Eq. (10) was an attempt to prepare that compound via exchange of an oxo ligand on tungsten with an alkylidene ligand on tantalum [49, 50]. Formation of **3** instead suggested that the oxo/alkylidene combination was a favorable one. Both the oxo ligand and the alkylidene ligand bound to a high oxidation state metal could be regarded as dianionic ligands. The 18-electron count in **3** is a consequence of π donation of one electron pair on the oxo ligand to the metal. In spite of the 18-electron count in **3**, it turned out to be a catalyst for the metathesis of terminal, as



well as internal, olefins (in benzene), but only in the presence of a trace of AlCl_3 . For the first time, the expected new alkylidene complexes could be observed; in several cases, including $\text{W}(\text{O})(\text{CH}_2)(\text{PMe}_3)_2\text{Cl}_2$, they could be isolated [39]. In the presence of one equivalent of AlCl_3 in dichloromethane, $\text{W}(\text{O})(\text{CH-t-Bu})(\text{PEt}_3)_2\text{Cl}_2$ yielded a complex that appeared to be $[\text{W}(\text{O})(\text{CH-t-Bu})(\text{PEt}_3)_2\text{Cl}][\text{AlCl}_4]$, and in the presence of two equivalents of AlCl_3 , an analogous dicationic species was formed [51]. Both would metathesize terminal and internal olefins in dichloromethane slowly (up to ~ 100 turnovers in 24 h). It was also shown that $\text{W}(\text{O})(\text{CH-t-Bu})(\text{PEt}_3)_2\text{Cl}_2$ could be isolated and that it would metathesize *cis*-2-pentene, although its activity was short-lived [49].

At approximately this time, important advances were made in the laboratories of J. A. Osborn at Strasbourg [4–8]. He found that addition of various Lewis acids to oxo neopentyl complexes yielded metathesis catalysts [8]. These were found to be transformed into oxo-free alkylidene complexes, $\text{W}(\text{CH-t-Bu})(\text{OCH}_2\text{-t-Bu})_2\text{Cl}_2$ (Eq. (11)) [4]. These in turn were



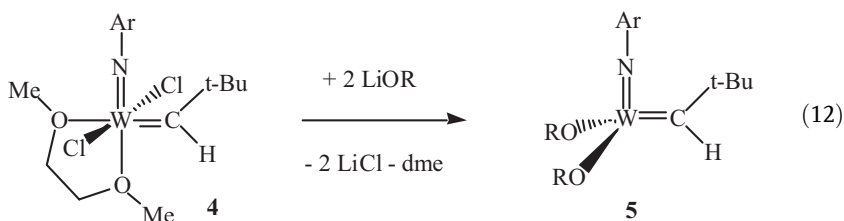
transformed by Lewis acids into cations of the type $[\text{W}(\text{CH-t-Bu})(\text{OCH}_2\text{-t-Bu})_2\text{X}]^+$ (e.g., as AlX_4^- salts) that were fully active for the metathesis of internal olefins and

that produced observable alkylidene intermediates [4]. These were the first studies in which rapid metathesis of olefins analogous to classical “black box” systems was observed, along with new alkylidenes, starting with a known d^0 alkylidene complex. Alkoxides (usually neopentoxides) were found to be crucial to the preparation and reactivity of tungsten-based metathesis catalysts of this type.

1.3.4

Development of Imido Alkylidene Complexes

In order to slow the intermolecular decomposition of an electronically unsaturated tungsten alkylidene complex, complexes that contained a sterically bulky imido ligand in place of the oxo ligand were sought. In order to maximize steric bulk but still limit the possibility of intramolecular CH activation reactions (e.g., in an ortho *t*-butyl group), the *N*-2,6-*i*-Pr₂C₆H₃ ligand was chosen. In this effort W(C-*t*-Bu)Cl₃(dme) (see chapter concerning alkylidyne complexes and alkyne metathesis in this volume) played an important role. Treatment of W(C-*t*-Bu)Cl₃(dme) with ArNH(TMS) (where Ar = 2,6-*i*-Pr₂C₆H₃) yielded W(C-*t*-Bu)(NHAr)Cl₂(dme). This compound could be converted into the related imido alkylidene complex **4** (Eq. (12)) by moving an α proton from nitrogen to carbon with the aid of a catalytic amount of triethylamine [52, 53]. Addition of bulky alkoxide ligands to **4** (OR = OMe₃, OMe(CF₃)₂, O-2,6-*i*-Pr₂C₆H₃, etc.) gave the 14-electron species W(NAr)(CH-*t*-Bu)(OR)₂ (assuming donation of one electron pair from the imido ligand). (Dimethoxyethane is retained in the coordination sphere of **5** only when the alkoxide is small and electron withdrawing, e.g., OCH(CF₃)₂.) The sterically bulky nature of all four ligands in **5** prevents bimolecular decomposition, a theme that harkens back to thermally stable (Me₃CCH₂)₃Ta=CHCMe₃.



Compounds of type **5** proved to be remarkably active catalysts for the metathesis of internal olefins [12, 14, 53]. The activity of such species for the metathesis of ordinary internal olefins (e.g., *cis*-2-pentene) appeared to maximize for the OMe(CF₃)₂ species. New alkylidene complexes (e.g., W(*N*-2,6-*i*-Pr₂C₆H₃)(CHPh)[OMe(CF₃)₂]₂, the X-ray structure of which is shown in Figure 1.3-1) could be isolated. Two types of tungstacyclobutane complexes, each of which had distinctive proton and carbon NMR spectra, could be observed under

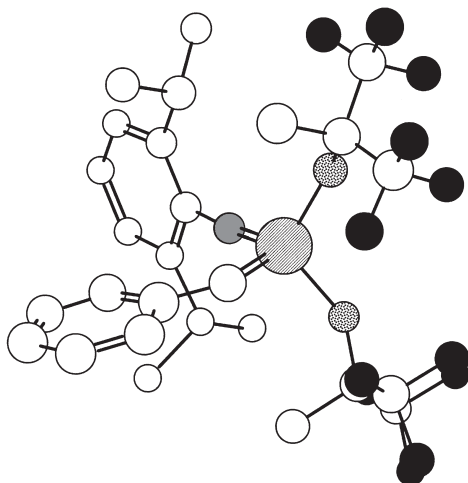


Fig. 1.3-1. Drawing of the structure of $W(N-2,6-i-Pr_2C_6H_3)(CHC_6H_5)[OCMe(CF_3)_2]_2$; $W=C = 1.859(22)$ Å, $W=N = 1.708(17)$ Å, $W-O = 1.903(16), 1.902(14)$ Å.

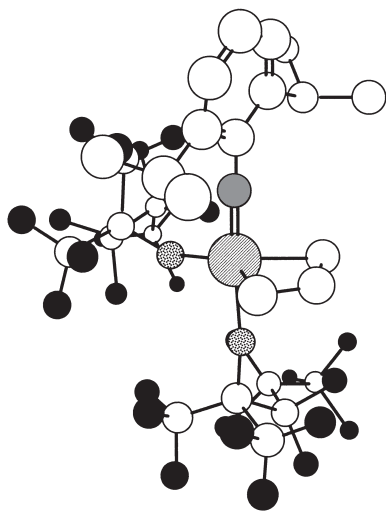


Fig. 1.3-2. Drawing of the structure of $W(N-2,6-i-Pr_2C_6H_3)(CH_2CH_2CH_2)[OC(CF_2CF_2CF_3)(CF_3)_2]_2$; $W-C_x = 2.064(22), 2.042(20)$ Å, $W=N = 1.748(15)$ Å.

a variety of circumstances [12]. X-ray studies showed that they were either trigonal bipyramidal (TBP) (e.g., **6a**; also see Figure 1.3-2) or square pyramidal (**6b**, see Figure 1.3-3). Square pyramidal species appeared to be the most stable toward loss

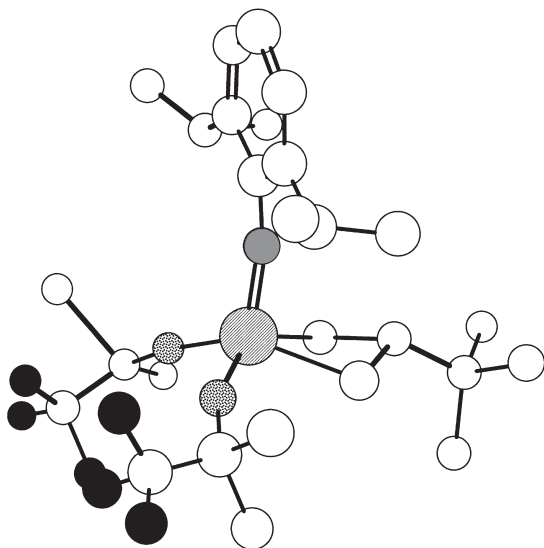
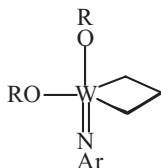
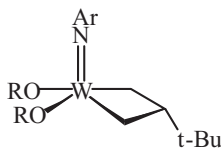


Fig. 1.3-3. Drawing of the structure of $W(N\text{-}2,6\text{-}i\text{-Pr}_2C_6H_3)[CH_2CH(t\text{-}Bu)CH_2][OCMe_2(CF_3)_2]_2$; $W\text{-}C_\alpha = 2.14(1)$, $2.17(1)$ Å, $W\text{-}N = 1.736(7)$ Å.



6a ($OR = OCMe_2(CF_3)_2$)



6b ($OR = OCMe_2(CF_3)_2$)

of olefin when the alkoxide was more electron donating, and TBP species appeared to be the most stable when the alkoxide was more electron withdrawing. However, steric factors perhaps were the most important determinants of metallacycle stability. It is not known which metallacycle, if either, is formed directly upon reaction of the alkylidene complex with an olefin, nor is the extent to which the two types of metallacycles can interconvert without loss of olefin known. However, in each type of metallacycle, the $M\text{-}C_\alpha$ bond lengths appeared to be relatively short, i.e. closer to metal-carbon double-bond lengths than to typical acyclic metal-carbon single-bond lengths. In any system in which ethylene is generated, unsubstituted metallacycles can be formed (e.g., as in Figure 1.3-2). They are the most stable toward loss of olefin for a variety of alkoxides. Methylene complexes of the type $W(NAr)(CH_2)(OR)_2$ could not be observed and are believed to decompose bimolecularly via formation of a species that contains two bridging methylene ligands. An important finding was that alkylidenes that contained β protons did not appear

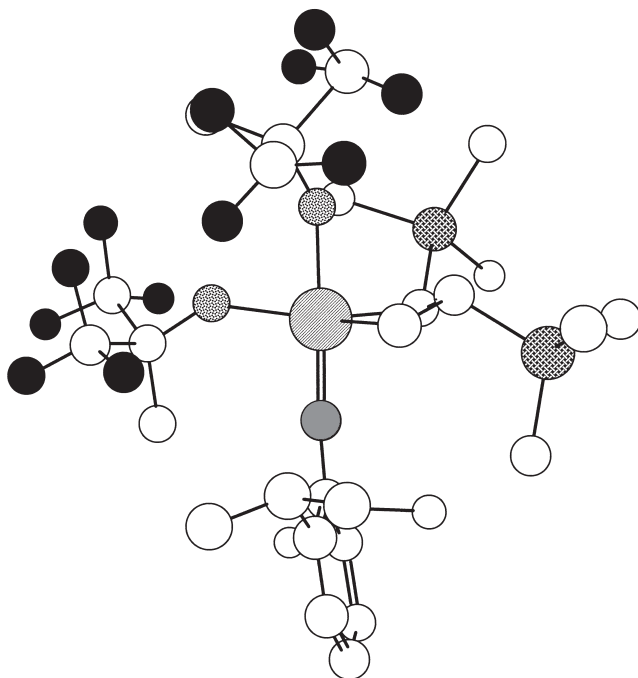
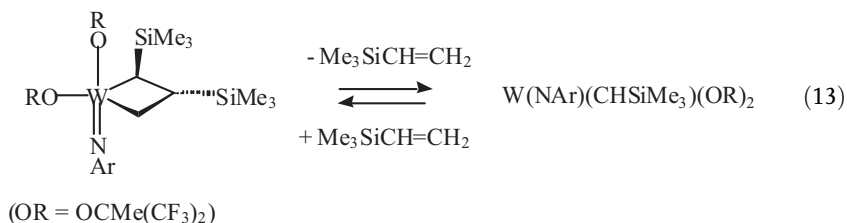
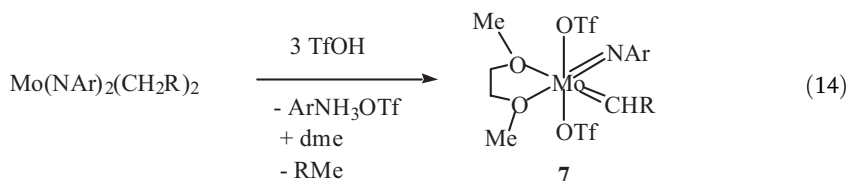


Fig. 1.3-4. Drawing of the structure of $W(N-2,6-i-Pr_2C_6H_3)[CH(SiMe_3)CH(SiMe_3)CH_2][OCMe(CF_3)_2]_2$; $W-C_{\alpha} = 2.066(11), 2.099(11) \text{ \AA}$, $W=N = 1.738(9) \text{ \AA}$.

to rearrange readily to olefins. A second important finding was that formation of a metallacyclobutane complex did not guarantee that an olefin would be metathesized. For example, reactions involving $Me_3SiCH=CH_2$ led to a TBP metallacyclobutane complex that could be isolated and structurally characterized (Eq. (13), Figure 1.3-4). It was shown to contain TMS groups that were *trans* with respect to one another and that were located on α and β carbon atoms. This is the type of intermediate that is required for formation of *trans*- $Me_3SiCH=CHSiMe_3$. However, this metallacycle apparently selectively loses $Me_3SiCH=CH_2$ (Eq. (13)). Therefore, $Me_3SiCH=CH_2$ is not metathesized to give ethylene and $Me_3SiCH=CHSiMe_3$.

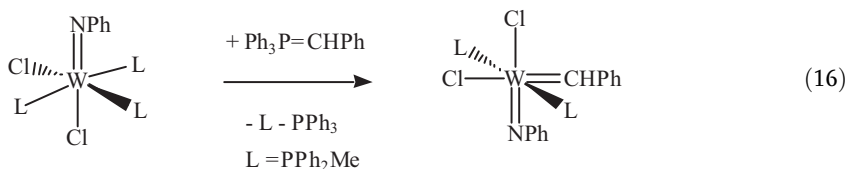
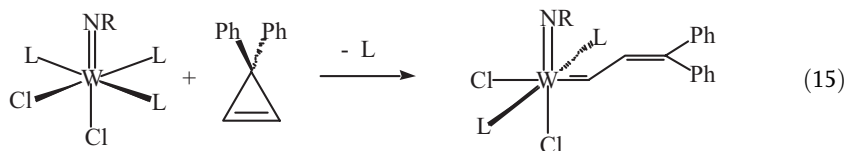


Attention then focused on molybdenum [54, 55] in the hope that molybdenum would be more tolerant of functionalities than tungsten. Molybdenum complexes analogous to **4** could be prepared from $\text{Mo}(\text{C}-t\text{-Bu})\text{Cl}_3(\text{dme})$, but since $(\text{Me}_3\text{CCH}_2)_3\text{Mo}\equiv\text{CCMe}_3$ (from which $\text{Mo}(\text{C}-t\text{-Bu})\text{Cl}_3(\text{dme})$ was prepared) could not be prepared reliably on a large scale, a new approach was required. The solution ultimately turned out to be the reaction shown in Eq. (14) ($\text{R} = t\text{-Bu}$ or CMe_2Ph) [56]. This reaction is remarkable for several reasons, one of them being the relative stability of **7** toward triflic acid. The intermediate in the reaction is believed to be $\text{Mo}(\text{NAr})(\text{CH}_2-t\text{-Bu})_2(\text{OTf})_2$, a five-coordinate species that contains five bulky ligands and in



which the metal is undoubtedly highly electron deficient. Therefore, α hydrogen abstraction to give $\text{Mo}(\text{NAr})(\text{CH}-t\text{-Bu})(\text{OTf})_2$ is facile. This unobservable four-coordinate species then binds dimethoxyethane strongly, leading to 18-electron **7** (including donation of the imido ligand's electron pair). Although **7** is relatively unreactive toward triflic acid, it reacts readily even with alkoxides that are poor nucleophiles (e.g., $\text{LiOCMe}(\text{CF}_3)_2$). This reaction sequence continues to be the favored method of synthesis of a wide variety of molybdenum imido neopentylidene or neophylidene ($\text{Mo}=\text{CHCMe}_2\text{Ph}$) complexes of the type $\text{Mo}(\text{CH}-t\text{-Bu})(\text{NAr})(\text{alkoxide})_2$. A variety of other imido groups have been employed [57], a fact that becomes important for further tuning of catalyst activity. Molybdenum complexes of the type $\text{Mo}(\text{NAr})(\text{CHCMe}_3)(\text{OR})_2$ also proved to be highly active for the metathesis of olefins, especially when the alkoxide ligand was the highly electron-withdrawing $\text{OCMe}(\text{CF}_3)_2$ ligand. One advantage of Mo versus W is that molybdacyclobutane intermediates generally lose olefin more readily than do tungstacyclobutane intermediates; therefore, molybdenum may be more active at lower temperatures than tungsten. In view of their instability toward olefin loss, molybdacyclobutane complexes in general cannot be isolated and structurally characterized.

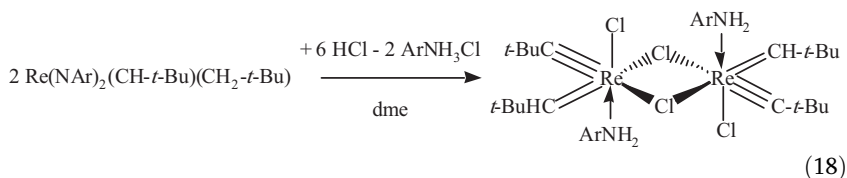
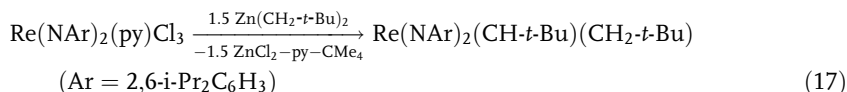
High oxidation state tungsten imido alkylidene complexes have been prepared by methods other than α hydrogen abstraction, two examples being rearrangement of a 3,3-diphenylcyclopropene [58] (Eq. (15); $\text{R} = 2,6\text{-Me}_2\text{C}_6\text{H}_3$ or $2,6\text{-i-Pr}_2\text{C}_6\text{H}_3$ and $\text{L} = \text{P}(\text{OMe})_3$ or PEt_2Ph) and alkylidene transfer from phosphorus [59–61] (Eq. (16)). It is not clear whether these methods are competitive with methods based upon α hydrogen abstraction for preparing tungsten catalysts. These alternative methods have not yet been extended to molybdenum.



1.3.5

Rhenium Alkylidene Complexes

A rhenium relative of Mo and W complexes of the type $\text{M}(\text{NAr})(\text{CH-}t\text{-Bu})(\text{OR})_2$ would be a $\text{Re}(\text{Y})(\text{CH-}t\text{-Bu})(\text{OR})_2$ complex in which Y is a sterically protected “3-” ligand, e.g., an alkylidene ligand. $\text{Re}(\text{CHCMe}_3)(\text{CCMe}_3)(\text{CH}_2\text{CMe}_3)_2$ has been found to be a stable species [62, 63], one that completes the list of neutral four-coordinate high oxidation state complexes of Ta, Mo, W, and Re that contain only neopentyl groups and ligands derived from neopentyl groups. A complex that contains two *t*-butoxides in place of two neopentyl groups, $\text{Re}(\text{CH-}t\text{-Bu})(\text{C-}t\text{-Bu})(\text{O-}t\text{-Bu})_2$ [62, 63], has also been prepared, but it proved to be unreactive toward representative olefins. (At that time the importance of electron-withdrawing alkoxides in metathesis was not fully appreciated.) The reactions shown in Eqs. (17) and (18) ultimately led to starting materials for the synthesis of $\text{Re}(\text{CHCMe}_3)(\text{CCMe}_3)(\text{OR})_2$ complexes in which OR could be varied widely [64–66]. The reaction in Eq. (18) is remarkable in the degree to which α protons on carbon and nitrogen are mobile and because in this circumstance the lowest

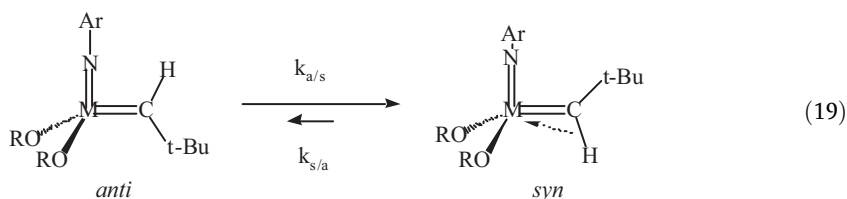


energy form contains a rhenium-carbon triple bond, not a rhenium-nitrogen pseudo triple bond. $\text{Re}(\text{CHCMe}_3)(\text{CCMe}_3)[\text{OCMe}(\text{CF}_3)_2]_2$ complexes ultimately proved to be active for olefin metathesis, although the rates are not as high as those for known Mo and W species [66], and new complications arose in some circumstances [67]. It remains to be seen whether well-defined rhenium complexes that are highly active for olefin metathesis in solution can be prepared.

1.3.6

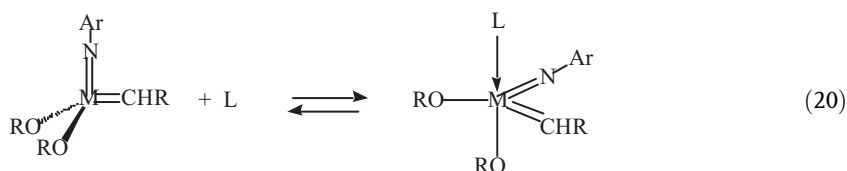
Details of Reactions of Imido Alkylidene Complexes and Theoretical Calculations

An important feature of all four-coordinate imido alkylidene Mo and W complexes is the formation of *syn* isomers, in which the alkylidene substituent points toward the imido ligand, or *anti* isomers, in which the alkylidene substituent points away from the imido ligand (e.g., Eq. (19)). The *syn* isomer is normally the one observed in the solid state and in solution. However, the rate at which these two isomers interconvert by rotation about the metal-carbon bond can vary dramatically as a function of the OR ligand, from $k_{s/a} \sim 1 \text{ s}^{-1}$ in the case of $\text{OR} = \text{OCMe}_3$ to $k_{s/a} \sim 10^{-5} \text{ s}^{-1}$ for $\text{OR} = \text{OCMe}(\text{CF}_3)_2$ in Mo imido complexes [68]. Therefore, both *syn* and *anti* species must be considered in any reaction scenario. Important questions include



whether a reaction involving the alkylidene ligand in either isomer is faster or slower than the rate of interconversion of isomers and whether one isomer is much more reactive than the other. A weak agostic interaction between the CH_x electron pair and the metal is believed to be a significant factor in stabilizing the *syn* form and possibly also reducing its reactivity. The consequences of the agostic interaction are a lower value for J_{CH_x} , a larger $\text{M}-\text{C}-\text{t-Bu}$ angle, and (when $\text{M} = \text{W}$) a larger value for the coupling between H_x and tungsten. Alkylidene α proton resonances are generally found in the region 10–15 ppm. In all *syn* complexes, the alkylidene proton resonance is found up-field of the *anti* alkylidene resonance in an analogous compound. It was proven in one case that the *anti* isomer reacted $\sim 10^5$ times more rapidly than the *syn* isomer (see later).

Imido alkylidene complexes readily form monoadducts with good electron donor ligands such as trimethylphosphine, pyridine, or quinuclidine. All structures so far have shown that the donor has added to the “CNO” tetrahedral face to yield a trigonal bipyramidal species in which the donor is located in the axial position (Eq. (20); Figure 1.3-5). When the alkoxide is relatively electron withdrawing (e.g., $\text{OCMe}(\text{CF}_3)_2$), when $\text{L} =$ trimethylphosphine, and when $\text{M} = \text{Mo}$, then the initial adduct contains the alkylidene in the *syn* orientation, the isomer that predominates in solution



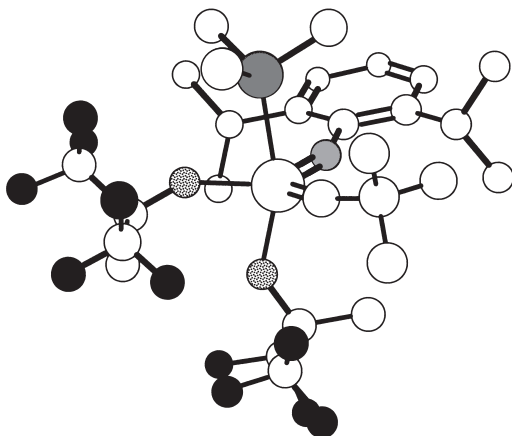
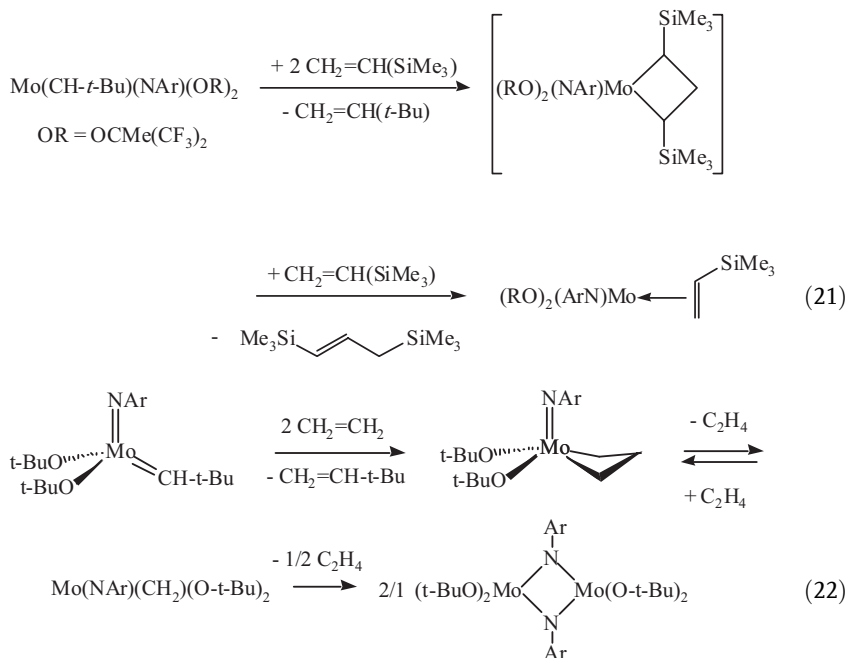


Fig. 1.3-5. Drawing of the structure of $\text{Mo}(\text{N}-2,6\text{-i-Pr}_2\text{C}_6\text{H}_3)(\text{CH-t-Bu})[\text{OCMe}(\text{CF}_3)_2]_2(\text{PMe}_3)$; $\text{W}=\text{C}_z = 1.878(9) \text{ \AA}$, $\text{W}=\text{N} = 1.767(6) \text{ \AA}$.

($K_{\text{eq}} \approx 2000$) for the four-coordinate hexafluoro-*t*-butoxide species. With time the *syn* adduct converts to the thermodynamically more stable *anti* adduct via loss of trimethylphosphine, rotation about the $\text{M}=\text{C}$ bond, and reassociation of trimethylphosphine. The *syn* adduct shown in Figure 1.3-5 shows a significant degree of steric interaction between the neopentylidene ligand and one ortho isopropyl group on the imido ligand, which is probably a factor in destabilizing the *syn* adduct relative to the *anti* adduct and in reducing its reactivity toward olefins. All evidence suggests that five-coordinate adducts are inactive for olefin metathesis since the donor ligand binds to the same orbital to which (it is presumed) the olefin binds. An alkylidene/olefin adduct, distinct from a metallacycle, has been observed by NMR at low temperatures in only one case, one that involved cationic catalysts of the type studied by Osborn [69]. In general, it is presumed that an alkylidene/olefin intermediate is a transition state on the pathway to formation of a metallacyclobutane species.

In a typical metathesis reaction, decomposition reactions (in addition to reactions with traces of water, oxygen, etc.) ultimately lead to catalyst death. The two main types of decompositions that have been elucidated are rearrangement of metallacyclobutane complexes to olefins and bimolecular decomposition of alkylidenes, especially methylene complexes. The reaction shown in Eq. (21) leads to formation of a Mo(IV) olefin complex as a consequence of rearrangement of an intermediate α,α' -disubstituted metallacyclobutane complex [70]. Upon reaction with ethylene, the analogous *t*-butoxide species yields an observable square pyramidal metallacyclobutane complex, which ultimately decomposes to yield a dimeric species that contains bridging imido groups (Eq. (22)). It is proposed that the dimer forms via a species that contains two bridging methylenes, which then loses ethylene. More recent studies involving binaphtholate complexes confirmed that some propylene is also formed upon decomposition of unsubstituted mo-

lybdacyclobutane complexes [71n]. Interestingly, decomposition of unsubstituted molybdacyclobutane complexes in the binaphtholate system appeared to be accelerated in both the presence of excess ethylene and the absence of excess ethylene.



Several aspects of Mo and W alkylidene complexes have been studied using theoretical methods [72]. Cundari and Gordon published three detailed papers in which *ab initio* methods were employed in order to study the principal resonance contributors to high oxidation state alkylidene complexes [72k], the effect of ligand and substituent modification [72l], and the nature of the olefin metathesis reaction with hypothetical Mo or W complexes of the type $\text{M}(\text{OH})_2(\text{NH})(\text{CH}_2)$ [72m]. They discovered that high oxidation state $\text{M}=\text{C}$ bonds are largely covalent with several major resonance contributors; therefore, viewing the $\text{M}=\text{C}$ bond as a simple $(+/-)$ polarized bond is a significant oversimplification. However, they also found that the intrinsic nature of the $\text{M}=\text{C}$ bond changes within relatively narrow limits as the ligands on M or the substituents on the alkylidene carbon are varied electronically. Finally, in hypothetical (simplified) metathesis catalysts they found (*inter alia*) that the $\text{Mo}=\text{C}$ π bond is the HOMO, that both *syn* and *anti* isomers are low energy forms, and that the “90°-rotated” alkylidene (in which the alkylidene substituents do not lie in the N-M-C plane) is relatively high in energy and is stabilized by bending of the $\text{Mo}=\text{N}-\text{H}$ bond in concert with electron pair donation from N to M.

The addition of ethylene to $\text{Mo}(\text{NH})(\text{CHR})(\text{OR}')_2$ ($\text{R} = \text{H}, \text{Me}$; $\text{OR}' = \text{CH}_3, \text{CF}_3$) was studied using both *ab initio* molecular orbital and density functional theory [72f]. Ethylene was found to favor attack on the CNO face of the pseudotetrahedral

alkylidene complex. The calculated activation energy for addition of ethylene when $R' = \text{CH}_3$ was significantly higher than when $R' = \text{CF}_3$. The *syn* alkylidene was found to be more stable than the *anti* alkylidene, perhaps because of an agostic interaction, although the transition state stabilities were similar. Therefore, the *anti* alkylidene is effectively the more reactive, as has been proposed on the basis of experimental studies described earlier.

The addition of ethylene to multiple metal-ligand bonds in $\text{Mo}(\text{E})\text{OCl}_2$ ($\text{E} = \text{S}, \text{Se}, \text{O}, \text{NH}, \text{PH}, \text{SiH}_2$, and CH_2) complexes has been studied using density functional methods [72g]. The ethylene was found to approach the metal most easily on the E-Mo-O face. The reaction was the most exothermic with the lowest barrier for $\text{E} = \text{SiH}_2$ followed by CH_2 and the other E's considered. The reactions were the least exothermic and had the highest barriers for $\text{E} = \text{O}$. These results rationalize why an olefin adds to an $\text{M}=\text{CHR}$ bond but not readily to an $\text{M}=\text{O}$ or an $\text{M}=\text{NR}$ bond, two other multiple bonds often found in alkylidene complexes.

Density functional methods also were used to study in detail how molybdacyclobutane complexes formed upon reaction of ethylene with complexes of the type $\text{L}_2\text{Mo}(\text{X})(\text{CH}_2)$ ($\text{X} = \text{O}, \text{NH}$; $\text{L} = \text{Cl}, \text{OCH}_3, \text{OCF}_3$) [72i]. The results of these calculations were consistent with the conclusions in other studies, namely the nature of the HOMO and LUMO, the relatively high energy of the rotated form of the alkylidene, and the effect of L upon the frontier orbitals. The authors also concluded that both trigonal bipyramidal and square pyramidal molybdacyclobutane species can form from the same basic transition state, with $\text{L} = \text{OCF}_3$ favoring the TBP molybdacycle and $\text{L} = \text{OCH}_3$ favoring the square pyramidal molybdacycle.

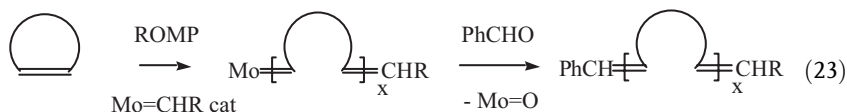
SCF-X α -SW calculations were carried out on $\text{Mo}(\text{VI})$ imido alkylidene complexes, $\text{Mo}(\text{NH})(\text{CH}_2)(\text{OH})_2$, $\text{Mo}(\text{NH})(\text{CH}_2)(\text{OCH}_3)_2$, and a complex in which the alkylidene ligand has been rotated by 90° [72n]. In $\text{Mo}(\text{NH})(\text{CH}_2)(\text{OH})_2$, the HOMO was identified as the Mo-C π -bond, and an agostic interaction involving the methylene proton pointing away from the imido ligand could be identified. The LUMO in $\text{Mo}(\text{NH})(\text{CH}_2)(\text{OH})_2$ was found to be the M-N π -anti-bonding orbital in the alkylidene plane, which is largely metal-centered on the COO face of the pseudotetrahedral complex. The electronic structure of $\text{Mo}(\text{NH})(\text{CH}_2)(\text{OCH}_3)_2$ is roughly the same as that for $\text{Mo}(\text{NH})(\text{CH}_2)(\text{OH})_2$. Bending of the imido proton toward the alkylidene ligand is an important stabilizing feature in the "rotated" alkylidene complex, lowering the activation energy for rotation by approximately 50%.

1.3.7

Catalyst and Reaction Variations

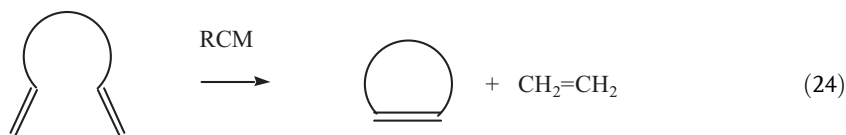
Several variations of the basic metathesis reaction have been explored with $\text{Mo}(\text{NAr})(\text{CHCMe}_3)(\text{OR})_2$ catalysts [14, 15]. In ring-opening metathesis polymerization (ROMP) reactions (first investigated using titanacyclobutane complexes [46, 47] and later tungsten [73] and molybdenum [74] imido alkylidene catalysts), a cyclic olefin such as a norbornene is attacked by the alkylidene to give a metallacyclobutane that opens to give a new alkylidene into which the cyclic species has

been incorporated [13, 46, 73–75]. If this step is irreversible, the new alkylidene can react with more cyclic olefin in a similar manner to form a polymer having repeating units that consist of the “opened” cyclic olefin (Eq. (23)). If no intermediate of this type decomposes during the process, then these ROMP reactions are “living.” Consequently, another monomer can be added after consumption of the first monomer and block copolymers prepared.

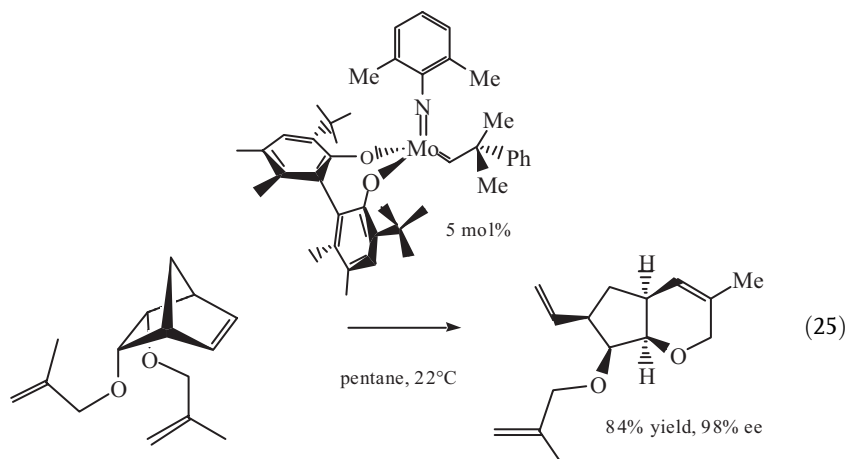


The polymer also can be cleaved from the metal in a Wittig-like reaction with a benzaldehyde. One of the more enlightening fundamental findings in this area was the elucidation of the origin of *cis* or *trans* double bonds in the ROMP polymer prepared from norbornenes (or disubstituted norbornadienes) and control of tacticity, i.e., the stereochemical relationship between neighboring repeat units in the ROMP polymer. It was found that the *syn* isomer gave rise to *cis* double bonds in the polymer, while the *anti* isomer gave rise to *trans* double bonds in the polymer [68]. It also was shown that catalysts of the type Mo(NAr)(CHCMe₃)(rac-diolate), where rac-diolate is a racemic chiral diolate such as a binaphtholate, can control the tacticity of the polymer to a remarkable degree by enantiomorphic site control [76]. In the process it also was proven that an all *cis* polymer was isotactic, while an all *trans* polymer was syndiotactic [77]. Perhaps most interesting from a fundamental point of view was the fact that the *anti* isomer in one circumstance was estimated to be $\sim 10^5$ times more reactive than the *syn* isomer, even though the *anti* isomer could not be observed at any point before or during the ROMP reaction [68]. The first enantiomerically pure molybdenum imido alkylidene complex was prepared in 1993 and employed for ROMP [77]. However, these “TADDOL” derivatives did not appear to be as stable as the 3,3′-disubstituted biphenoxide or binaphtholate derivatives described below.

Another important variation of a metathesis reaction is ring-closing metathesis (RCM), the simplest schematic version of which is shown in Eq. (24). RCM reactions catalyzed by Mo(NAr)(CHCMe₂Ph)[OCMe(CF₃)₂]₂ were shown in 1992 to be a remarkably facile and “clean” means of forming a variety of cyclic olefins [78]. Many papers have appeared in the last several years in which Mo(NAr)(CHCMe₂Ph)[OCMe(CF₃)₂]₂ is the catalyst for RCM [15], although since ~ 1995 a variety of ruthenium carbene complexes [79–86], which are best viewed as Ru(II) species, have been employed more often. (See Chapter 1.6).



Recent additions to the arsenal of molybdenum catalyst systems are those that contain a variety of enantiomerically pure biphenolate or binaphtholate ligands and one of several different imido ligands. Such species have been shown to catalyze a variety of enantioselective ring-closing, ring-opening, and cross-metathesis reactions efficiently [71]. (See Chapter 2.3) An example is shown in Eq. (25) [71e]. Analogous enantiomerically pure catalysts

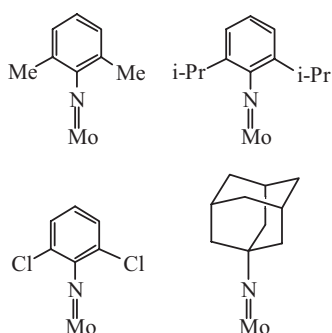


that contain the $\{(R,R)\text{-}1,2\text{-}[\text{OC}(\text{CF}_3)_2\text{CH}_2]_2\text{C}_5\text{H}_8\}$ ligand were found to be inefficient catalysts in several kinetic resolutions of comparable substrates [87, 88].) The modular nature of molybdenum catalysts (i.e., the ability to vary the imido and diolate ligands) is an important asset that leads to maximum efficiency. Rapid interconversion of *syn* and *anti* isomers [71f] allows both isomers to be available for enantioselective reactions and presumably allows one to react more rapidly and (it is hoped) in a more enantioselective manner. Asymmetric metathesis reactions hold considerable promise as a means of relatively quickly preparing enantiomerically pure organic compounds from simple starting materials; in many cases such products could not be prepared readily by any other combination of methods [71i]. Some of the imido ligands and diolates currently in use for preparing asymmetric catalysts for enantioselective reactions are shown in Scheme 1.3-1 [71i].

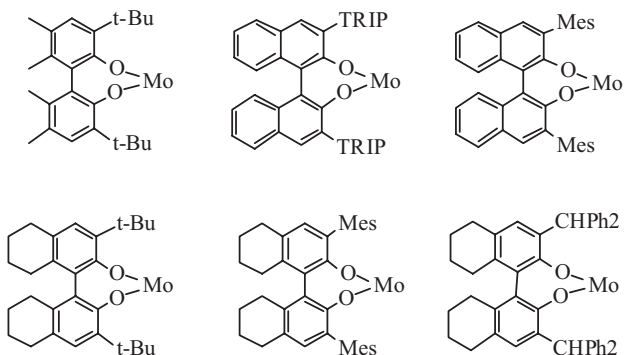
Molybdenum imido alkylidene complexes also have been employed for a variety of other catalytic reactions of interest to the organic or polymer chemist, among them selective cross-couplings of olefins [89], polymerization of terminal alkynes [90–92], step-growth polymerization of dienes [93, 94], and cyclopolymerization of 1,6-heptadiynes [95–97].

It is clear that electron-withdrawing alkoxides in $\text{M}(\text{NAr})(\text{CHR})(\text{OR}')_2$ complexes dramatically increase the rate of reaction of an olefin with the $\text{M}=\text{CHR}$ bond. In fact, no other X ligands in $\text{M}(\text{NAr})(\text{CHR})\text{X}_2$ complexes are as successful as alk-

Imido Groups



Diolates

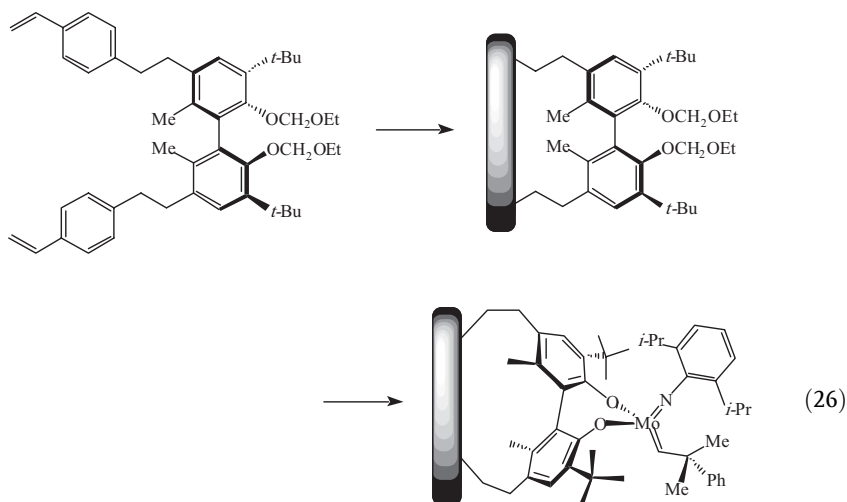


Scheme 1.3-1. Some of the imido groups and diolates currently in use in asymmetric metathesis reactions.

oxides for sustained metathesis activity [16], either because they are not bulky enough to stabilize an electron-deficient metal center and prevent bimolecular decomposition (e.g., halides) or because they donate too much electron density to the metal in a σ and/or π fashion (e.g., amides or thiolates). A recent example of an unreactive complex is $\text{Mo}(\text{NAr})(\text{CHR})(\text{diamide})$, where the diamide is a N,N' -disubstituted-2,2'-bisamido-1,1'-binaphthyl ligand; no ready reaction was observed between this complex and ethylene or even benzaldehyde [98].

Recent studies have shown that it is possible to prepare asymmetric catalysts *in situ* in THF and that these catalysts perform as well as isolated catalysts in various asymmetric reactions [71k]. This approach has important practical implications and also suggests that rapid throughput screening methods may be viable for testing catalysts of this general type.

A catalyst that is attached to a support also could have practical value in terms of catalyst screening and, if the support is rigid enough, possibly also in preventing bimolecular reactions of methylene complexes and thereby extending catalyst lifetime. The first example of a supported asymmetric metathesis catalyst has now been reported [71p]. The protected biphenolate ligand shown in Eq. (26) can be polymerized by free radical methods in the presence of styrene to yield cross-linked polystyrene that contains the protected ligand incorporated as part of the polymer. Deprotection of the ether, deprotonation of the biphenol, and addition of $\text{Mo}(\text{CHCMe}_2\text{Ph})(\text{NAr})(\text{OTf})_2(\text{dme})$ then lead to a catalyst that is chemically linked to the polymer backbone. The supported catalyst was shown to behave as efficiently in terms of %ee as the homogeneous analogue in several asymmetric metathesis reactions, although the rate was slower, as expected. The supported catalyst also could be recycled, although its activity decreased with time. If bimolecular decomposition reactions of methylene complexes are to be eliminated, then absolutely rigid supports (e.g., silica) may be required.



1.3.8

Concluding Remarks

I have attempted to trace highlights of the discovery and development imido alkylidene catalysts of Mo and W, the high oxidation state species that have been the most successful in the metathesis of olefins. Many of the principles of high oxidation state alkylidene chemistry were established first for tantalum, while the development of high oxidation state alkylidyne complexes of W and Mo and alkyne metathesis by them cemented the connection between metathesis of alkynes and the metathesis of alkenes by sterically protected, four-coordinate high oxidation state Mo and W species that contain alkoxide ligands. Metathesis by high oxidation state rhenium complexes has not yet reached the level of activity that is observed with Mo and W species, and Re is not as accessible as Mo and W. Two attractive features of the reaction are the facts that a metathesis reaction can replace several traditional organic synthesis steps and at the same time can generate a whole new approach to synthesis of an organic molecule. Olefin metathesis, especially in terms of applications in organic and polymer chemistry, promises to continue to be an attractive and exciting area of research.

Acknowledgments

I thank the National Science Foundation for supporting research on multiple metal-carbon bonds for many years and, more recently, the National Institutes of Health for supporting work on organic applications of asymmetric metathesis in collaboration with A. Hoveyda. I also thank the many coworkers who have been involved in this research for their hard work and enthusiasm.

References

- 1 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, 1997.
- 2 HÉRRISON, J. L.; CHAUVIN, Y. *Makromol. Chem.* **1971**, 141, 161.
- 3 (a) FISCHER, E. O. *Pure Appl. Chem.* **1970**, 24, 407. (b) FISCHER, E. O. *Pure Appl. Chem.* **1972**, 30, 353. (c) FISCHER, E. O. *Adv. Organometal. Chem.* **1976**, 14, 1.
- 4 KRESS, J.; WESOLEK, M.; OSBORN, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 514.
- 5 KRESS, J.; AGUERO, A.; OSBORN, J. A. *J. Mol. Catal.* **1986**, 36, 1.
- 6 YOUINOU, M. T.; KRESS, J.; FISCHER, J.; AGUERO, A.; OSBORN, J. A. *J. Am. Chem. Soc.* **1988**, 110, 1488.
- 7 KRESS, J. R. M.; RUSSELL, M. J. M.; WESOLEK, M. G.; OSBORN, J. A. *J. Chem. Soc., Chem. Commun.* **1980**, 431.
- 8 KRESS, J.; WESOLEK, M.; LE NY, J.-P.; OSBORN, J. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1039.
- 9 COUTURIER, J. L.; PAILLET, C.; LECONTE, M.; BASSET, J. M.; WEISS, K. *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 628.
- 10 LEFEBVRE, F.; LECONTE, M.; PAGANO, S.; MUTCH, A.; BASSET, J.-M. *Polyhedron* **1995**, 14, 3209.
- 11 SCHROCK, R. R. in *Reactions of Coordinated Ligands*; BRATERMAN, P. R., Ed.; Plenum: New York, 1986.
- 12 FELDMAN, J.; SCHROCK, R. R. *Prog. Inorg. Chem.* **1991**, 39, 1.
- 13 SCHROCK, R. R. in *Metathesis Polymerization of Olefins and Polymerization of Alkynes*; IMAMOGLU, Y., Ed.; Kluwer, 1998, pp 1.
- 14 SCHROCK, R. R. in *Topics in Organometallic Chemistry. Alkene Metathesis in Organic Synthesis*; FÜRSTNER, A., Ed.; Springer: Berlin, 1998; Vol. 1, pp 1.
- 15 SCHROCK, R. R. *Tetrahedron* **1999**, 55, 8141.
- 16 SCHROCK, R. R. *Polyhedron* **1995**, 14, 3177.
- 17 SCHROCK, R. R. *Pure Appl. Chem.* **1994**, 66, 1447.
- 18 SCHROCK, R. R. *Chem. Rev.* **2002**, 102, 145.
- 19 FISCHER, E. O.; MAASBÖL, A. *Angew. Chem., Int. Ed. Engl.* **1964**, 3, 580.
- 20 TEBBE, F. N.; PARSHALL, G. W.; REDDY, G. S. *J. Am. Chem. Soc.* **1978**, 100, 3611.
- 21 OTT, K. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1981**, 103, 5922.
- 22 JUVINALL, G. L. *J. Am. Chem. Soc.* **1964**, 86, 4202.
- 23 SCHMIDBAUR, H. *Adv. Organometal. Chem.* **1976**, 14, 205.
- 24 SHORTLAND, A. J.; WILKINSON, G. J. *Chem. Soc., Dalton Trans.* **1973**, 872.
- 25 SCHROCK, R. R.; MEAKIN, P. J. *Am. Chem. Soc.* **1974**, 96, 5288.
- 26 SCHROCK, R. R. *J. Organometal. Chem.* **1976**, 122, 209.
- 27 SCHROCK, R. R. *J. Am. Chem. Soc.* **1974**, 96, 6796.
- 28 SCHROCK, R. R. *J. Am. Chem. Soc.* **1976**, 98, 5399.
- 29 SCHROCK, R. R. *J. Am. Chem. Soc.* **1975**, 97, 6577.
- 30 SCHROCK, R. R.; SHARP, P. R. *J. Am. Chem. Soc.* **1978**, 100, 2389.
- 31 SCHROCK, R. R.; GUGGENBERGER, L. J. *J. Am. Chem. Soc.* **1975**, 97, 6578.
- 32 TAKUSAGAWA, F.; KOETZLE, T. F.; SHARP, P. R.; SCHROCK, R. R. *Acta Cryst.* **1988**, C44, 439.
- 33 BROOKHART, M.; GREEN, M. L. H.; WONG, L. *Prog. Inorg. Chem.* **1988**, 36, 1.
- 34 CHAMBERLAIN, L. R.; HUFFMAN, J. C.; ROTHWELL, I. P. *J. Am. Chem. Soc.* **1986**, 108, 1502.
- 35 RUPPRECHT, G. A.; MESSERLE, L. W.; FELLMANN, J. D.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1980**, 102, 6236.
- 36 SCHULTZ, A. J.; WILLIAMS, J. M.; SCHROCK, R. R.; RUPPRECHT, G. A.; FELLMANN, J. D. *J. Am. Chem. Soc.* **1979**, 101, 1593.
- 37 WOOD, C. D.; McLAIN, S. J.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1979**, 101, 3210.
- 38 McLAIN, S. J.; WOOD, C. D.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1979**, 101, 4558.
- 39 SCHROCK, R. R.; ROCKLAGE, S. M.; WENGROVIUS, J. H.; RUPPRECHT, G.; FELLMANN, J. J. *Molec. Catal.* **1980**, 8, 73.

- 40 ROCKLAGE, S. M.; FELLMANN, J. D.; RUPPRECHT, G. A.; MESSERLE, L. W.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 1440.
- 41 HOWARD, T. R.; LEE, J. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876.
- 42 LEE, J. B.; GAJDA, G. J.; SCHAEFER, W. P.; HOWARD, T. R.; IKARIYA, T.; STRAUS, D. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 7358.
- 43 STRAUS, D. A.; GRUBBS, R. H. *Organometallics* **1982**, *1*, 1658.
- 44 TEBBE, F. N.; PARSHALL, G. W.; OVENALL, D. W. *J. Am. Chem. Soc.* **1979**, *101*, 5074.
- 45 TEBBE, F. N.; HARLOW, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 6149.
- 46 GRUBBS, R. H.; TUMAS, W. *Science* **1989**, *243*, 907.
- 47 GILLIOM, L. R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 733.
- 48 SHARP, P. R.; SCHROCK, R. R. *J. Organometal. Chem.* **1979**, *171*, 43.
- 49 WENGROVIUS, J. H.; SCHROCK, R. R.; CHURCHILL, M. R.; MISSERT, J. R.; YOUNGS, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 4515.
- 50 CHURCHILL, M. R.; RHEINGOLD, A. L.; YOUNGS, W. J.; SCHROCK, R. R. *J. Organometal. Chem.* **1981**, *204*, C17.
- 51 WENGROVIUS, J. H.; SCHROCK, R. R. *Organometallics* **1982**, *1*, 148.
- 52 SCHAEVERIEN, C. J.; DEWAN, J. C.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 2771.
- 53 SCHROCK, R. R.; DePUE, R.; FELDMAN, J.; SCHAEVERIEN, C. J.; DEWAN, J. C.; LIU, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423.
- 54 MURDZEK, J. S.; SCHROCK, R. R. *Organometallics* **1987**, *6*, 1373.
- 55 SCHROCK, R. R.; KROUSE, S. A.; KNOLL, K.; FELDMAN, J.; MURDZEK, J. S.; YANG, D. C. *J. Molec. Catal.* **1988**, *46*, 243.
- 56 SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DiMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
- 57 OSKAM, J. H.; FOX, H. H.; YAP, K. B.; McCONVILLE, D. H.; O'DELL, R.; LICHTENSTEIN, B. J.; SCHROCK, R. R. *J. Organometal. Chem.* **1993**, *459*, 185.
- 58 JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8130.
- 59 JOHNSON, L. K.; FREY, M.; ULIBARRI, T. A.; VIRGIL, S. C.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8167.
- 60 JOHNSON, L. K.; VIRGIL, S. C.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 5384.
- 61 BUIJINK, J. K.; TEUBEN, J. H.; KOIJMAN, H.; SPEK, A. L. *Organometallics* **1994**, *13*, 2922.
- 62 EDWARDS, D. S.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 6806.
- 63 EDWARDS, D. S.; BIONDI, L. V.; ZILLER, J. W.; CHURCHILL, M. R.; SCHROCK, R. R. *Organometallics* **1983**, *2*, 1505.
- 64 TOREKI, R.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 2448.
- 65 TOREKI, R.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1992**, *114*, 3367.
- 66 TOREKI, R.; VAUGHAN, G. A.; SCHROCK, R. R.; DAVIS, W. M. *J. Am. Chem. Soc.* **1993**, *115*, 127.
- 67 VAUGHAN, G. A.; TOREKI, R.; SCHROCK, R. R.; DAVIS, W. M. *J. Am. Chem. Soc.* **1993**, *115*, 2980.
- 68 OSKAM, J. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11831.
- 69 KRESS, J.; OSBORN, J. A. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 1585.
- 70 ROBBINS, J.; BAZAN, G. C.; MURDZEK, J. S.; O'REGAN, M. B.; SCHROCK, R. R. *Organometallics* **1991**, *10*, 2902.
- 71 (a) ALEXANDER, J. B.; LA, D. S.; CEFALO, D. R.; HOVEYDA, A.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041. (b) LA, D. S.; ALEXANDER, J. B.; CEFALO, D. R.; GRAF, D. D.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720. (c) ZHU, S. S.; CEFALO, D. R.; LA, D. S.; JAMIESON, J. Y.; DAVIS, W. M.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251. (d) LA, D. S.; FORD, J. G.; SATTELY, E. S.; BONITATEBUS, P. J.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603. (e) WEATHERHEAD, G. S.; FORD, J. G.; ALEXANIAN, E. J.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828. (f) ALEXANDER, J. B.; SCHROCK, R. R.; DAVIS, W. M.;

- HULTZSCH, K. C.; HOVEYDA, A. H.; HOUSER, J. H. *Organometallics* **2000**, *19*, 3700. (g) DOLMAN, S. J.; SATTELY, E. S.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991. (h) WEATHERHEAD, G. S.; HOUSER, J. H.; FORD, J. G.; JAMIESON, J. Y.; SCHROCK, R. R.; HOVEYDA, A. H. *Tet. Lett.* **2000**, *49*, 9553. (i) HOVEYDA, A. H.; SCHROCK, R. R. *Chem. Eur. J.* **2001**, *7*, 945. (j) CEFALO, D. R.; KIELY, A. F.; WUCHRER, M.; JAMIESON, J. Y.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139. (k) AEILTS, S. L.; CEFALO, D. R.; BONITATEBUS, P. J.; HOUSER, J. H.; HOVEYDA, A. H.; SCHROCK, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452. (l) LA, D. S.; SATTELY, E. S.; FORD, J. G.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767. (m) HULTZSCH, K. C.; BONITATEBUS, P. J., JR.; JERNELIUS, J.; SCHROCK, R. R.; HOVEYDA, A. H. *Organometallics* **2001**, *20*, 4705. (n) TSANG, W. C. P.; SCHROCK, R. R.; HOVEYDA, A. H. *Organometallics* **2001**, *20*, 5568. (o) SCHROCK, R. R.; JAMIESON, J. Y.; DOLMAN, S. J.; MILLER, S. A.; BONITATEBUS, P. J., JR.; HOVEYDA, A. H. *Organometallics* **2002**, *21*, 409. (p) HULTZSCH, K. C.; JERNELIUS, J. A.; HOVEYDA, A. H.; SCHROCK, R. R. *Angew. Chem. Int. Ed.* **2002**, 589–593. (q) KIELY, A. F.; JERNELIUS, J. A.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868.
- 72** (a) MARYNICK, D. S.; KIRKPATRICK, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 1993. (b) SODUPE, M.; LLUCH, J. M.; OLIVA, A.; BERTRAN, J. *Organometallics* **1989**, *8*, 1837. (c) UPTON, T.; RAPPE, A. K. *J. Am. Chem. Soc.* **1985**, *107*, 1206. (d) USHIO, J.; NAKATSUJI, H.; YONEZAWA, T. *J. Am. Chem. Soc.* **1984**, *106*, 5892. (e) SODUPE, M.; LLUCH, J. M.; OLIVA, A.; BERTRAN, J. *Nouv. J. Chim.* **1991**, *15*, 321. (f) WU, Y.-D.; PENG, Z.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8043. (g) MONTEYNE, K.; ZIEGLER, T. *Organometallics* **1998**, *17*, 5901. (h) CHOI, S.-H.; LIN, Z.; XUE, Z. *Organometallics* **1999**, *18*, 5488. (i) FOLGA, E.; ZIEGLER, T. *Organometallics* **1993**, *12*, 325. (j) EISENSTEIN, O.; HOFFMANN, R.; ROSSI, A. R. *J. Am. Chem. Soc.* **1981**, *103*, 5582. (k) CUNDARI, T. R.; GORDON, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 5231. (l) CUNDARI, T. R.; GORDON, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 539. (m) CUNDARI, T. R.; GORDON, M. S. *Organometallics* **1992**, *11*, 55. (n) FOX, H. H.; SCHOFIELD, M. H.; SCHROCK, R. R. *Organometallics* **1994**, *13*, 2804. (o) VYBOISHCHIKOV, S. F.; FRENKING, G. *Chem. Eur. J.* **1998**, *4*, 1428. (p) VYBOISHCHIKOV, S. F.; FRENKING, G. *Chem. Eur. J.* **1998**, *4*, 1439. (q) GODDARD, R. J.; HOFFMANN, R.; JEMMIS, E. D. *J. Am. Chem. Soc.* **1980**, *102*, 7667.
- 73** SCHROCK, R. R.; FELDMAN, J.; CANNIZZO, L.; GRUBBS, R. H. *Macromolecules* **1987**, *20*, 1169.
- 74** SCHROCK, R. R. in *Ring-Opening Polymerization*; BRUNELLE, D. J., Ed.; Hanser: Munich, 1993, pp 129.
- 75** BUCHMEISER, M. R. *Chem. Rev.* **2000**, *100*, 1565.
- 76** TOTLAND, K. M.; BOYD, T. J.; LAVOIE, G. G.; DAVIS, W. M.; SCHROCK, R. R. *Macromolecules* **1996**, *29*, 6114.
- 77** MCCONVILLE, D. H.; WOLF, J. R.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 4413.
- 78** (a) FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (b) FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.
- 79** (a) FÜRSTNER, A. *Topics in Catalysis* **1997**, *4*, 285. (b) FÜRSTNER, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (c) GRUBBS, R. H.; MILLER, S. J.; FU, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (d) SCHUSTER, M.; BLECHERT, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2037. (e) SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039. (f) SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
- 80** HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSON, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.
- 81** SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. *Tetrahedron Letters* **1999**, *40*, 2247.

- 82 ACKERMANN, L.; FÜRSTNER, A.; WESKAMP, T.; KOHL, F. J. *Tet. Lett.* **1999**, 40, 4787.
- 83 WESKAMP, T.; KOHL, F. J.; HIERINGER, W.; GLIECH, D.; HERRMANN, W. A. *Angew. Chem. Int. Ed.* **1999**, 38, 2416.
- 84 KINGSBURY, J. S.; HARRITY, J. P. A.; BONITATEBUS, P. J.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, 121, 791.
- 85 GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, 122, 8168.
- 86 (a) WESKAMP, T.; SCHATTEMMANN, W. S. C.; SPIEGLER, M.; HERRMANN, W. A. *Angew. Chem. Int. Ed.* **1998**, 37, 2490. (b) FÜRSTNER, A.; PICQUET, M.; BRUNEAU, C.; DIXNEUF, P. H. *Chem. Commun.* **1998**, 1315. (c) HANSEN, S. M.; ROMINGER, F.; METZ, M.; HOFMANN, P. *Chem. Eur. J.* **1999**, 5, 557. (d) HANSEN, S. M.; VOLLAND, M. A. O.; ROMINGER, R.; EISENTRÄGER, F.; HOFFMANN, P. *Angew. Chem. Int. Ed.*, 38, 1273. (e) HERRMANN, W. A.; SCHATTEMMANN, W. C.; NUYKEN, O.; GLANDER, S. C. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1087. (f) BUCHOWICZ, W.; MOL, J. C.; LUTZ, M.; SPEK, A. L. *J. Organomet. Chem.* **1999**, 588, 205. (g) KATAYAMA, H.; OZAWA, F. *Organometallics* **1998**, 17, 5190. (h) DEL RIO, I.; VAN KOTEN, G. *Tetrahedron Lett.* **1999**, 40, 1401. (i) LINDNER, E.; PAUTZ, S.; FAWZI, R.; STEIMANN, M. *Organometallics* **1998**, 17, 3006. (j) NUBEL, P. O.; HUNT, C. L. *J. Mol. Catal. A* **1999**, 40, 323.
- 87 FUJIMURA, O.; DE LA MATA, F. J.; GRUBBS, R. H. *Organometallics* **1996**, 15, 1865.
- 88 FUJIMURA, O.; GRUBBS, R. H. *J. Org. Chem.* **1998**, 63, 824.
- 89 (a) CROWE, W. E.; ZHANG, Z. J. *J. Am. Chem. Soc.* **1993**, 115, 10998. (b) CROWE, W. E.; GOLDBERG, D. R. *J. Am. Chem. Soc.* **1995**, 117, 5162. (c) CROWE, W. E.; GOLDBERG, D. R.; ZHANG, Z. J. *Tetrahedron Lett.* **1996**, 37, 2117.
- 90 MASUDA, T.; TACHIMORI, H. J. *Macromol. Sci. Pure Appl. Chem.* **1994**, A31, 1675.
- 91 SCHROCK, R. R.; LUO, S.; ZANETTI, N.; FOX, H. H. *Organometallics* **1994**, 13, 3396.
- 92 SCHROCK, R. R.; LUO, S.; LEE, J. C. J.; ZANETTI, N. C.; DAVIS, W. M. *J. Am. Chem. Soc.* **1996**, 118, 3883.
- 93 (a) THORN-CSANYI, E.; PFLUG, K. P. *Makromol. Chem., Rapid Commun.* **1993**, 14, 619. (b) THORN-CSANYI, E.; KRAXNER, P. *Macromol. Rapid Commun.* **1995**, 16, 147.
- 94 (a) KONZELMAN, J.; WAGENER, K. B. *Macromolecules* **1995**, 28, 4686. (b) KONZELMAN, J.; WAGENER, K. B. *Macromolecules* **1996**, 29, 7657. (c) WAGENER, K. B.; BRZEZINSKA, K.; ANDERSON, J. D.; YOUNKIN, T. R.; STEPPE, K.; DEBOER, W. *Macromolecules* **1997**, 30, 7363.
- 95 CHOI, S.-K.; GAL, Y.-S.; JIN, S.-H.; KIM, H. K. *Chem. Rev.* **2000**, 100, 1645.
- 96 FOX, H. H.; SCHROCK, R. R. *Organometallics* **1992**, 11, 2763–2765.
- 97 FOX, H. H.; WOLF, M. O.; O'DELL, R.; LIN, B. L.; SCHROCK, R. R.; WRIGHTON, M. S. *J. Am. Chem. Soc.* **1994**, 116, 2827.
- 98 JAMIESON, J. Y.; SCHROCK, R. R.; DAVIS, W. M.; BONITATEBUS, P. J.; ZHU, S. S.; HOVEYDA, A. H. *Organometallics* **2000**, 19, 925.

1.4

From Ill-Defined to Well-Defined W Alkylidene Complexes

Christophe Copéret, Frédéric Lefebvre, and Jean-Marie Basset

Dedicated to M. Leconte

1.4.1

Introduction

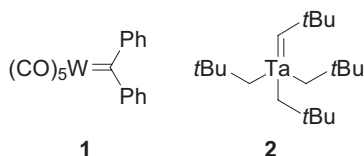
The tremendous industrial and academic efforts in the area of olefin valorization, (particularly in the area of polymerization) in conjunction with the development in the early 1960s of organometallic chemistry led to the discovery of olefin metathesis. The catalytic systems were either group 6 metals supported on oxide support (such as WO_3/SiO_2 used industrially for the transformation of propene into ethylene and butene) or group 6 metal chlorides such WCl_6 combined with an alkylating agent with Lewis acidic properties ($\text{AlX}_n\text{R}_{3-n}$, SnR_4 , ...) [1], a system derived from the Ziegler-Natta olefin polymerization catalytic system.

When Chauvin proposed and established the widely accepted carbene mechanism, the reaction of WCl_6 and various alkylating agents gave ill-defined systems, and carbene intermediates were elusive. For example, the first homogeneous metathesis system disclosed by Calderon including WCl_6 , ethanol, and an alkylating agent (EtAlCl_2) in a 1:1:4 ratio already supported the idea that the coordination sphere could involve alkoxides and carbene ligands (arising from the two alkyl groups via an α -H abstraction step) [2]. The first well-defined metallocarbene used in olefin metathesis was the Casey derivative $[\text{Ph}_2\text{C}=\text{W}(\text{CO})_5]$ [3], and the discovery of nucleophilic carbenes by Schrock led to the development of a variety of well-defined group 5–8-based metallocarbenes (Scheme 1.4-1) [4]. We will describe the development of well-defined W-based metallocarbenes with a special focus on their alkoxy derivatives [5].

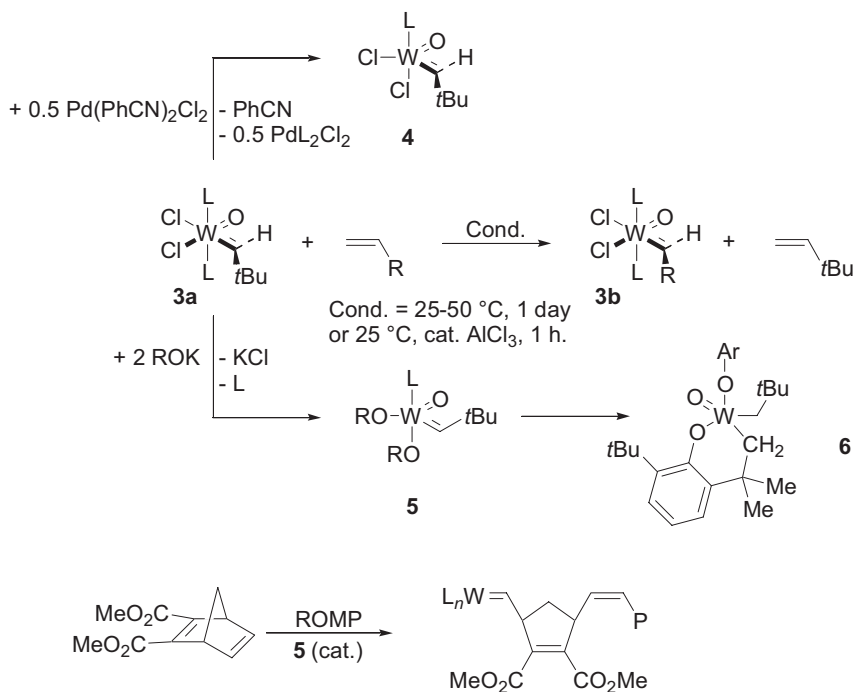
1.4.2

Oxoalkylidene W Complexes

The first example of a well-defined (Schrock) alkylidene W complex is probably $[\text{Cl}_2\text{W}(\text{=O})(=\text{CH}t\text{Bu})(\text{PR}_3)_2]$ (**3a**) [6]. While **3a** only slowly exchanged its alkyl-

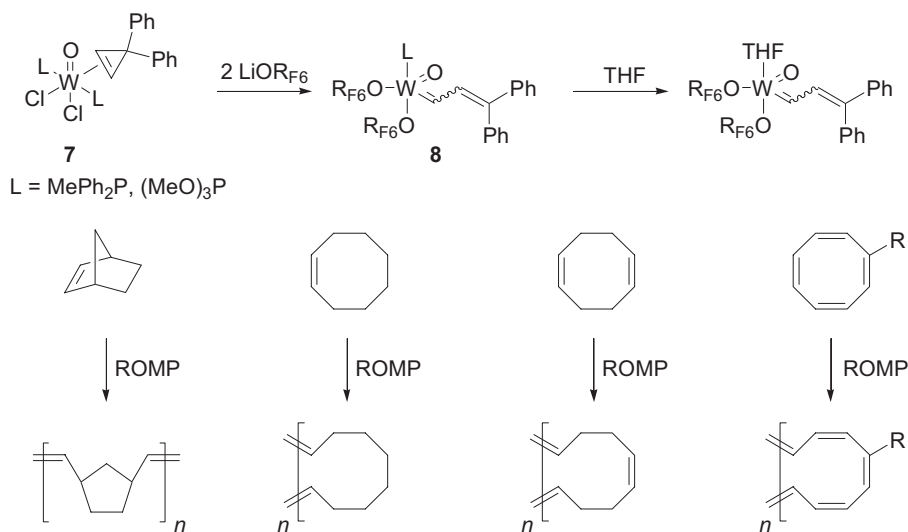


Scheme 1.4-1



Scheme 1.4-2. Well-defined oxoalkylidene W complexes.

dene ligands with olefins, the addition of co-catalysts such as AlCl_3 accelerated this reaction, but that catalytic system proved to be very unstable. Moreover, since these species did not have a coordination site readily available, Schrock et al. worked on removing one of the phosphine ligands. Therefore, the reaction of **3a** with phosphine sponge (a Pt benzonitrile complex) allowed the generation of a penta-coordinated complex **4**, $[\text{Cl}_2\text{W}(=\text{O})(=\text{CHtBu})(\text{PR}_3)]$, which has been fully characterized and which is an olefin metathesis catalyst without the need of a co-catalyst. Nonetheless, this system still displayed extreme instability, which prevented good productivity [7]. The use of aryloxy ligands can also provide monophosphine penta-coordinated complexes (**5**; $\text{ArO} = 2,6\text{-diphenylphenoxide}$; Scheme 1.4-2), which are highly active living polymerization catalysts in ROMP [8]. For example, ROMP of 2,3-dicarbomethoxynorbornadiene gave polymers of



Scheme 1.4-3. Oxovinylalkylidene W complexes.

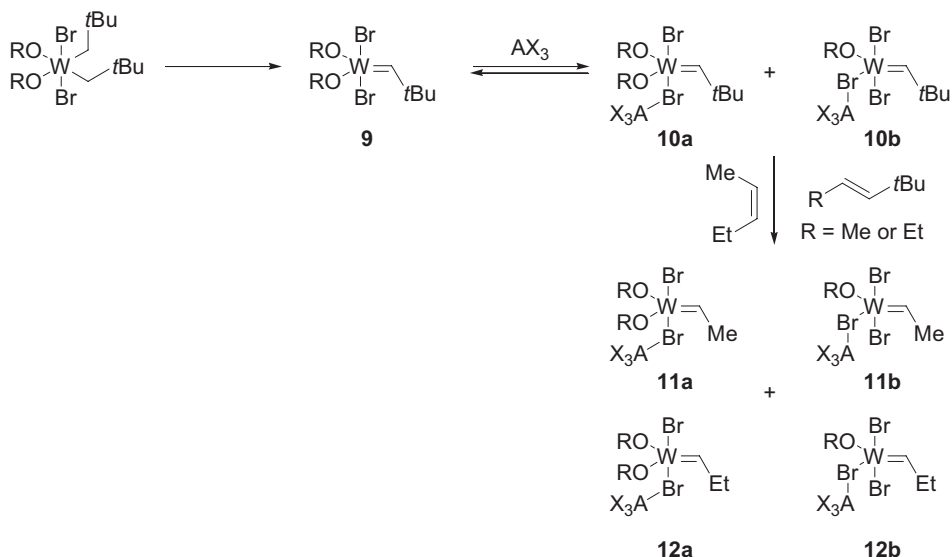
low polydispersity and high stereoselectivity (>95% *cis*; Scheme 1.4-3). The substituents on the aryloxy ligand could also play an important role; for example, the *o,o'*-*t*Bu derivatives were readily converted into the cyclometallated product **6**, which was inactive in olefin metathesis.

Additionally, Grubbs et al. have shown that it is possible to prepare phosphite or base-free oxoalkylidene W complexes by using another synthetic route starting from **7** (Scheme 1.4-3). The resulting complex (**8**) was active in ROMP of various cycloolefins, even for the less reactive cyclooctatetraene, which provides a polyacetylene material [9, 10].

1.4.3

Alkoxy-Alkylidene W Complexes: Kress-Osborn System

In parallel, Osborn used di(alkyl) W complexes as an entry to well-defined alkylidene W complexes such as **9** (Scheme 1.4-4) [11]. While these alkylidene species showed no activity in *cis* 2-pentene metathesis by themselves, addition of Lewis acids such as AlBr_3 or GaBr_3 generated highly active species (**10**) that readily catalyzed olefin metathesis at room temperature (1000 equivalents of *cis* 2-pentene converted in 1 min). Moreover, it was possible to observe the alkylidene exchange when the addition of the olefin was performed at lower temperatures. Therefore, upon mixing *cis* 2-pentene at -10°C with **10**, new alkylidene complexes **11** and **12** were formed in a 1-to-4 ratio. Noteworthy was the fact that the formation of the active species depended highly on the ligands surrounding W. For example, the tribromoalkoxy derivatives, $[\text{Br}_3(\text{tBuCH}_2\text{O})\text{W}(=\text{CHtBu})]$, were more

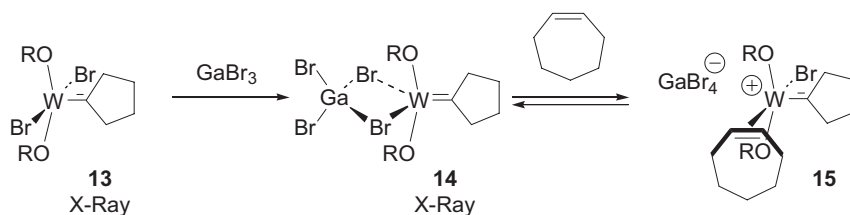


Scheme 1.4-4. Osborn's system and its reactivity towards olefins.

Tab. 1.4-1. Initial rates of *cis* 2-pentene (mol/mol W/min) using $[(RO)_xBr_{(4-x)}W(=CHtBu)]$.

Catalysts	Without LA	With 2 equivalents of $GaBr_3$
$[(RO)Br_3W(=CHtBu)]$	40	800
$[(RO)_2Br_2W(=CHtBu)]$	0.5	1700
$[(RO)_3BrW(=CHtBu)]$	Low	3500
$[(RO)_4W(=CHtBu)]$	0	Low

active than **9** in the absence of Lewis acid, while in the presence of $GaBr_3$ the monobromotris(alkoxy) complex, $[Br(tBuCH_2O)_3W(=CHtBu)]$, was the most active system (Table 1.4-1) [12]. On the other hand, the tetrakis(alkoxy)alkylidene $[(tBuCH_2O)_4W(=CHtBu)]$ systems were much less reactive, even in the presence of Lewis acids [13]. The cyclopentylidene system allowed us to obtain crystals suitable for X-ray studies and showed that **13** and the Lewis acid adduct **14** had roughly the same structures, the latter having one longer $W-Br$ bond, thus giving a penta-coordinated system slightly perturbed by an extra ligand [14]. Rapid Br ligand exchange in **14** was observed in solution, and the fully cationic species was probably formed in solution, explaining the high activity of **13** in the presence of Lewis acids. Therefore, when cycloheptene was contacted at 177 K with a solution of **14** (Scheme 1.4-5), a π -olefin complex **15** was observed by NMR spectroscopy, and the investigation of the associated equilibrium constants at various temperatures (220–



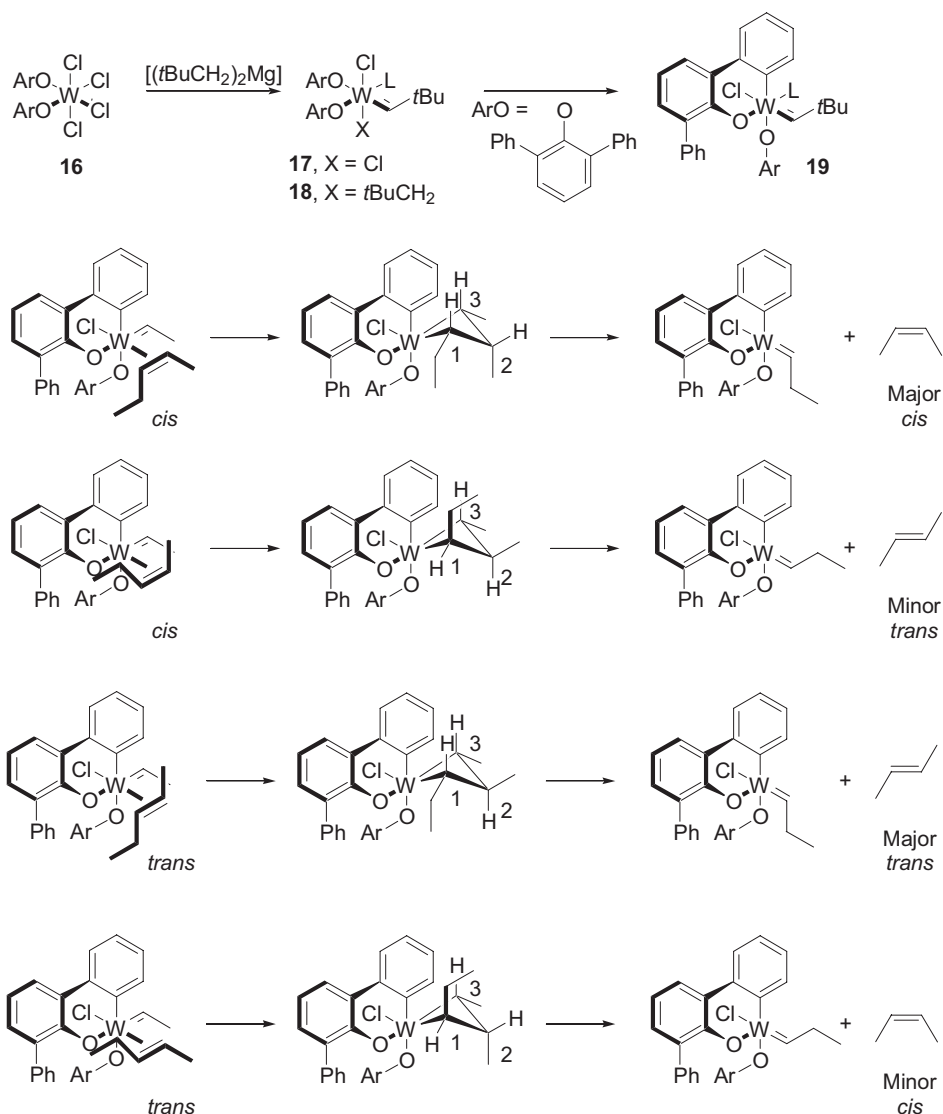
Scheme 1.4-5. Well-defined cationic alkylidene W complex and its reactivity with cycloheptene.

245 K) provided thermodynamic data for the complexation reaction $\Delta H = -13.6$ kcal mol^{−1} and $\Delta S = -55$ cal.mol^{−1} K^{−1}, as well as an activation Gibbs energy of 10.6 kcal.mol^{−1}. Upon increasing the reaction temperature to 255 K, the ring-opening polymerization started [15].

1.4.4

Aryloxy-Alkylidene W Complexes: Leconte-Basset System

In the meantime, the preparation of well-defined aryloxytungsten complexes [(ArO)_xWCl_(6-x)] appeared [16] and provided access to another class of sterically and electronically tunable tungsten centers. The reaction of [(ArO)₂WCl₄] with 1 and 1.5 equivalents of [(*t*BuCH₂)₂Mg · dioxane] provided [(ArO)₂W(=CH*t*Bu)Cl₂(OR₂)] and [(ArO)₂W(=CH*t*Bu)(CH₂*t*Bu)Cl(OR₂)], respectively (Scheme 1.4-6) [17]. In the special case of the *o,o'*-diphenylphenoxy ligand, the product rearranges to give **19** via cyclometallation to form another well-defined alkylidene in which the cyclometallation occurs via the formation of a sigma bond between the aromatic substituent of the phenoxy and the tungsten. This complex displays good activity in olefin metathesis (500 equivalents of *cis* 2-pentene equilibrated in 1 min), but more importantly, this reaction is stereospecific (>99% stereoselectivity), i.e., *cis* gives *cis* and *trans* gives *trans* (Figure 1.4-1, Scheme 1.4-6). This high stereoselectivity is probably related to the relative stability of metallocyclobutanes in which [1,3]-interactions have to be minimized. Conversely, the ROMP of 1-methylnorbornene provides a completely head-to-tail, predominantly syndiotactic polymer with 100% *cis* double bond (Scheme 1.4-7) [18]. Moreover, this system is compatible with a wide range of functional groups [19], i.e., alkylsilanes, alkylstannanes, esters, ethers, and, more surprisingly, phosphanes and thioethers in both RCM and self-metathesis or ROMP reactions (Schemes 1.4-8 and 1.4-9). The self- and cross-metathesis of allylsulfide, as well as the ROMP of 5-alkylthiocyclooctene, have been especially documented. In the latter reaction, it was found that the choice of the alkyl substituents was critical to obtaining high TOF and TON, and large alkyl groups such as cyclohexyl and *t*Bu prevented a significant decrease in reaction rate, probably via destabilization of **20**. Finally, this catalyst catalyzes the self-metathesis of very oxygen-rich molecules, such as the glucosides having various protecting groups (PG), e.g., acetyl or *t*-butyldimethylsilyl PG (Scheme 1.4-10) [20].



Scheme 1.4-6. Preparation of **19** and its stereoselectivity in olefin metathesis.

1.4.5

Amidoalkylidene W Complexes

A related class of metallocarbene is based on the substitution of alkoxide by amide ligands [21]. The complexes are prepared from the corresponding dichlorides by alkylation to form a dialkyl complex (**21**), which, in the presence of trimethylphosphane, can be transformed into the monophosphine adduct **24** (Scheme 1.4-11). This complex catalyzes the ROMP of norbornene and the ADMET of 1,9-decadiene.

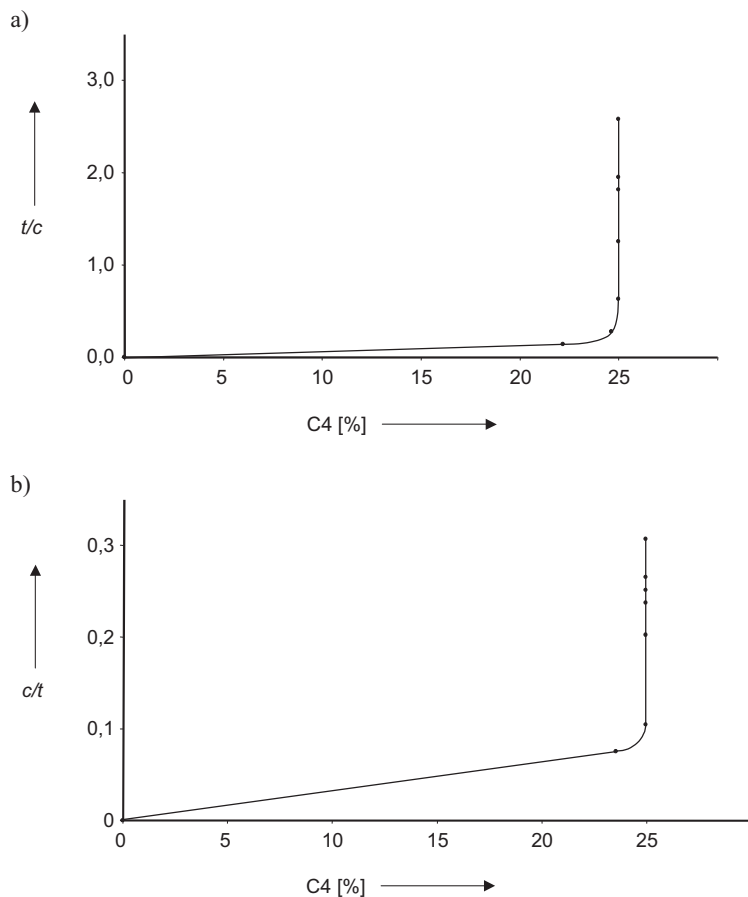
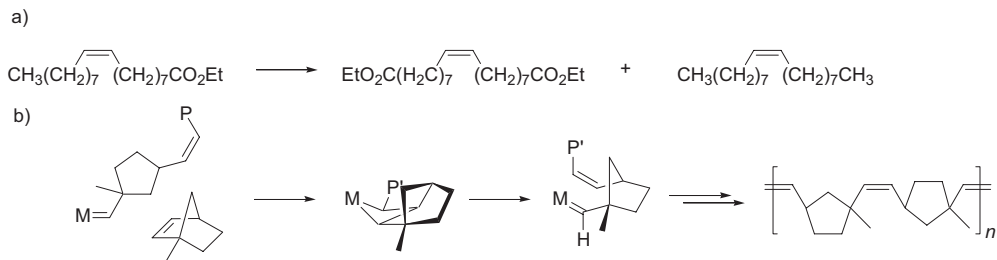
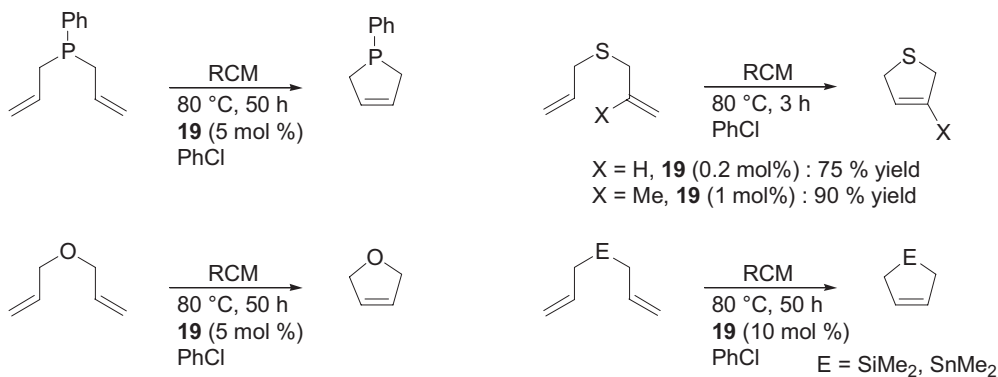
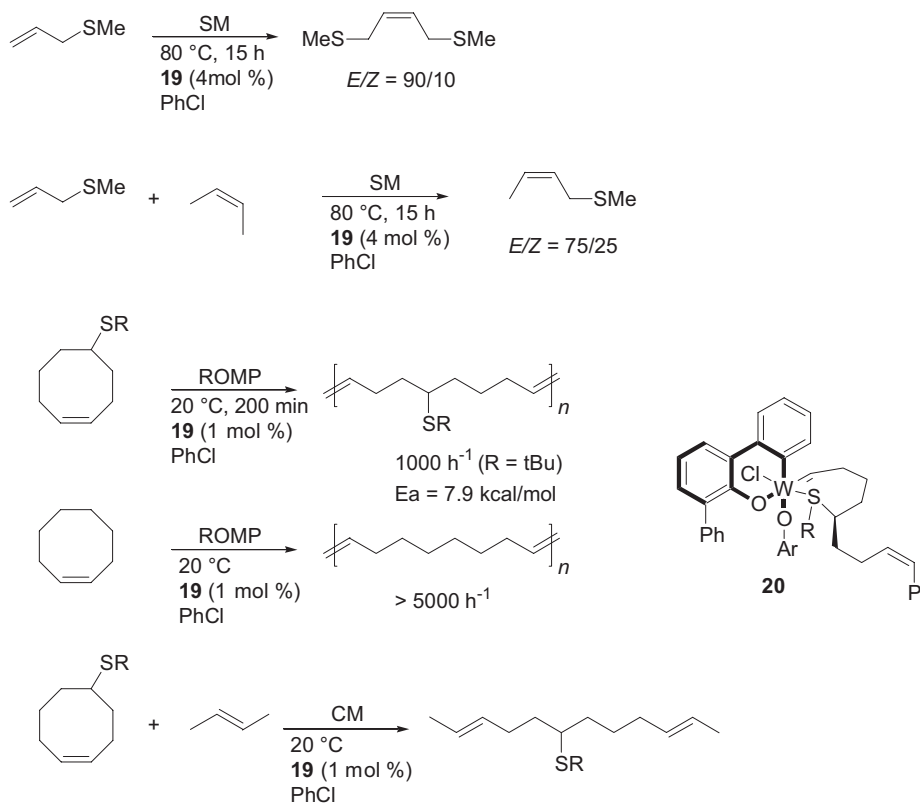
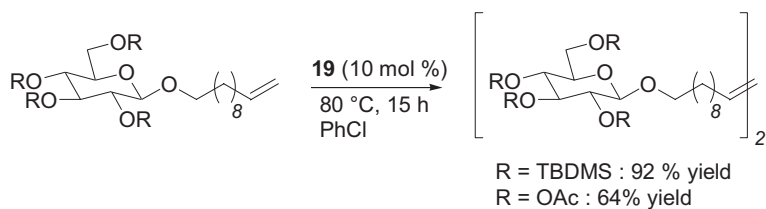


Fig. 1.4-1. a) Plot of the ratio of *trans* to *cis* 2-butene (t/c) vs. the conversion in butene in the metathesis of *cis* 2-pentene by **19**. b) Plot of the ratio of *cis* to *trans* 2-butene (c/t) vs. the conversion in butene in the metathesis of *trans* 2-pentene by **19**.

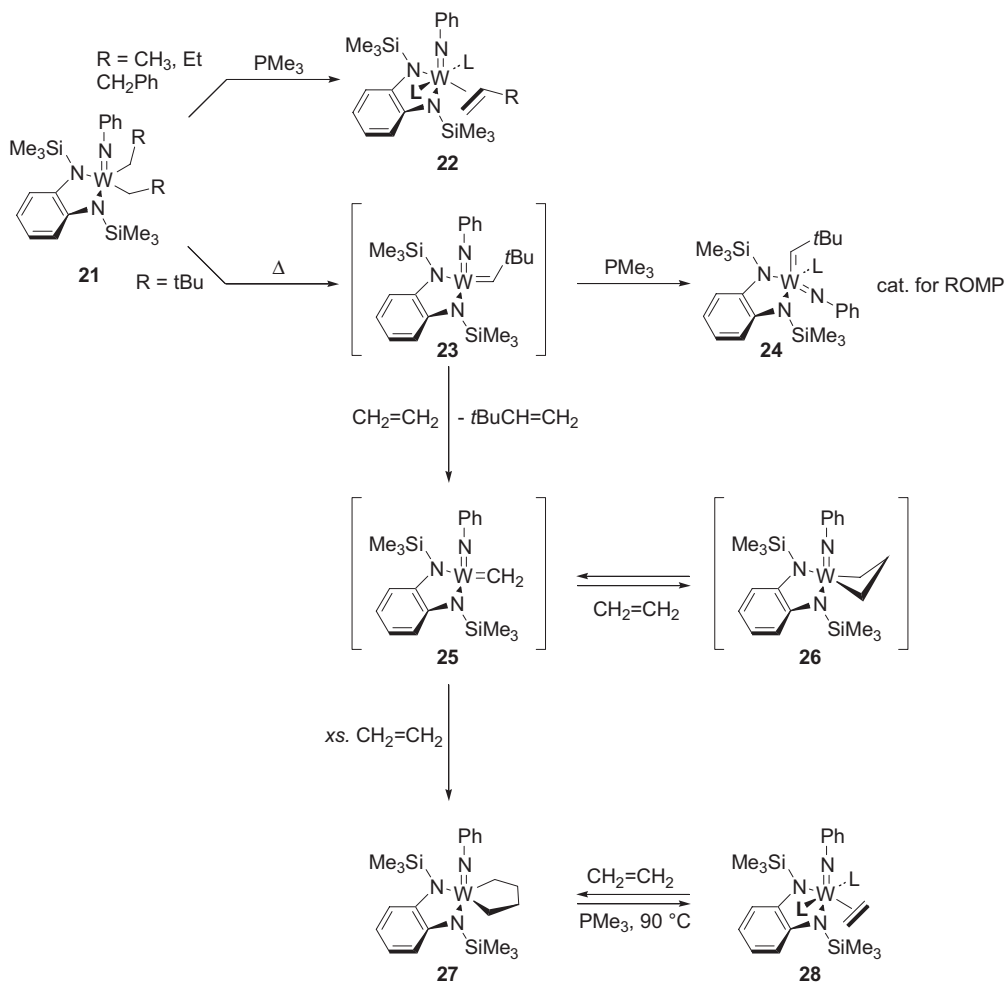


Scheme 1.4-7. Reactivity of **19** in olefin metathesis.

Scheme 1.4-8. Reactivity of **19** in RCM.Scheme 1.4-9. Reactivity of **19** towards sulfide containing olefins.



Scheme 1.4-10. Reactivity of **19** towards glucosides.



Scheme 1.4-11. Amidoiminoalkylidene W complex.

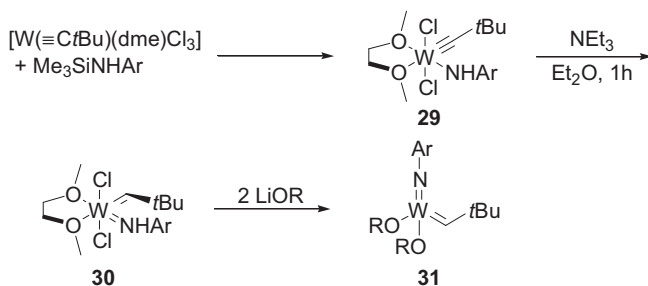
The reaction of the parent dialkyl with ethylene in the presence or in the absence of phosphane ligands is noteworthy, e.g., the reaction of ethylene that gives the cross-metathesis product ($t\text{BuCH}=\text{CH}_2$) along with the metallacyclopentane **27**. In the presence of phosphane, the ethylene adduct **28** is observed. Moreover, it is possible to observe the metallacyclobutane **26**, which then decomposes to give the metallacyclopentane in the presence of ethylene. This decomposition pathway could be related to the propensity of the dialkyl complex to undergo β -H abstraction to form an olefin-metal complex that can readily react with ethylene (formation of **22**). Moreover, methylenecarbene can also readily decompose by dimerization and be reduced. Both pathways can explain the formation of metallacyclopentane intermediates, which could be a potential deactivation pathway for homogeneous olefin metathesis catalysts.

1.4.6

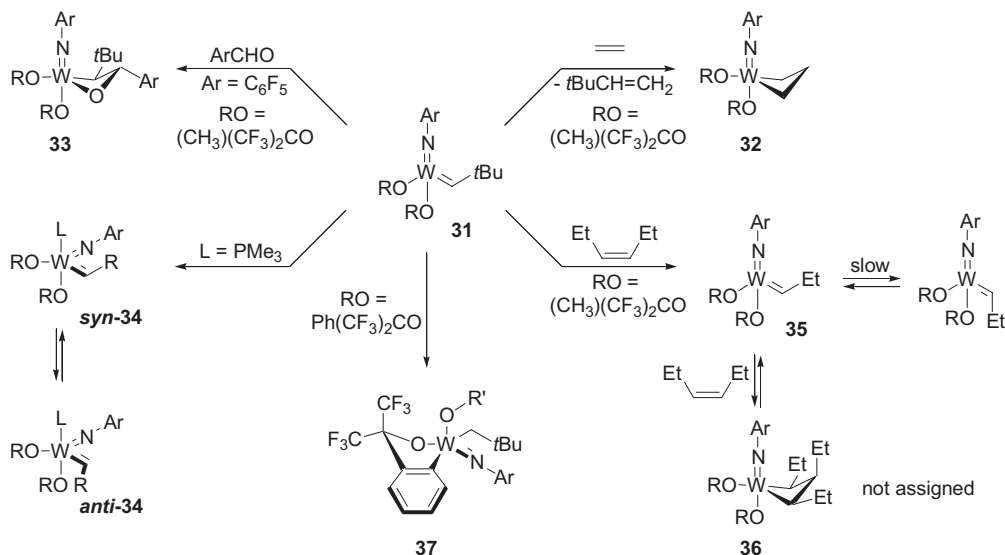
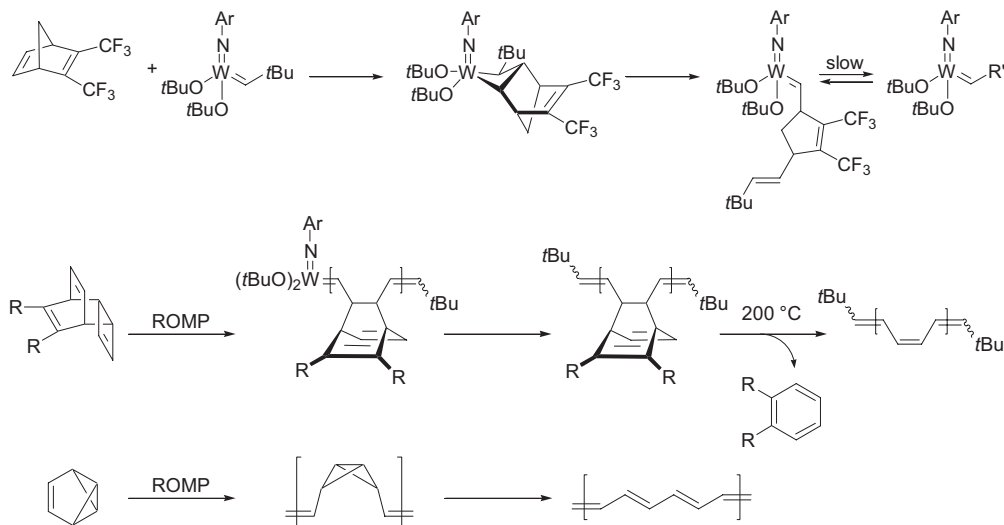
Imido-Alkylidene W Complexes: Schrock's System

Based on the promising results obtained with the oxo ligand, the imido family was developed, since the better π -bonding ability of this ligand could increase stability [22]. This led to the preparation of the well-defined, base-free W-alkylidene complex **31**, $[(\text{RO})_2\text{W}(\text{CH}t\text{Bu})(=\text{NAr})]$ (Scheme 1.4-12) [23]. This system turned out to be a highly active olefin metathesis catalyst, and it transforms 3700 equivalents of *cis* 2-pentene in <5 min at 25 °C in the absence of a co-catalyst. It even catalyzes the metathesis of methyl oleate (200–300 equivalents). Complex **31** reacts with ethylene to give the corresponding metallacyclobutane intermediate **32** and ($t\text{BuCH}=\text{CH}_2$) (Scheme 1.4-13) [24]. The corresponding reaction with pentafluorobenzaldehyde gives the oxometallacyclobutane **33**, which then decomposes into olefin and the oxo-imido complex [25]. Addition of PMe_3 on **31** yields *syn*-**34**, which slowly transforms into *anti*-**34**, the thermodynamic product.

Moreover, *cis* 3-hexene is converted into its metathesis product (*trans* 3-hexene) along with 1 equivalent of 5,5-dimethyl-3-hexene. The propylidene W complex **35**

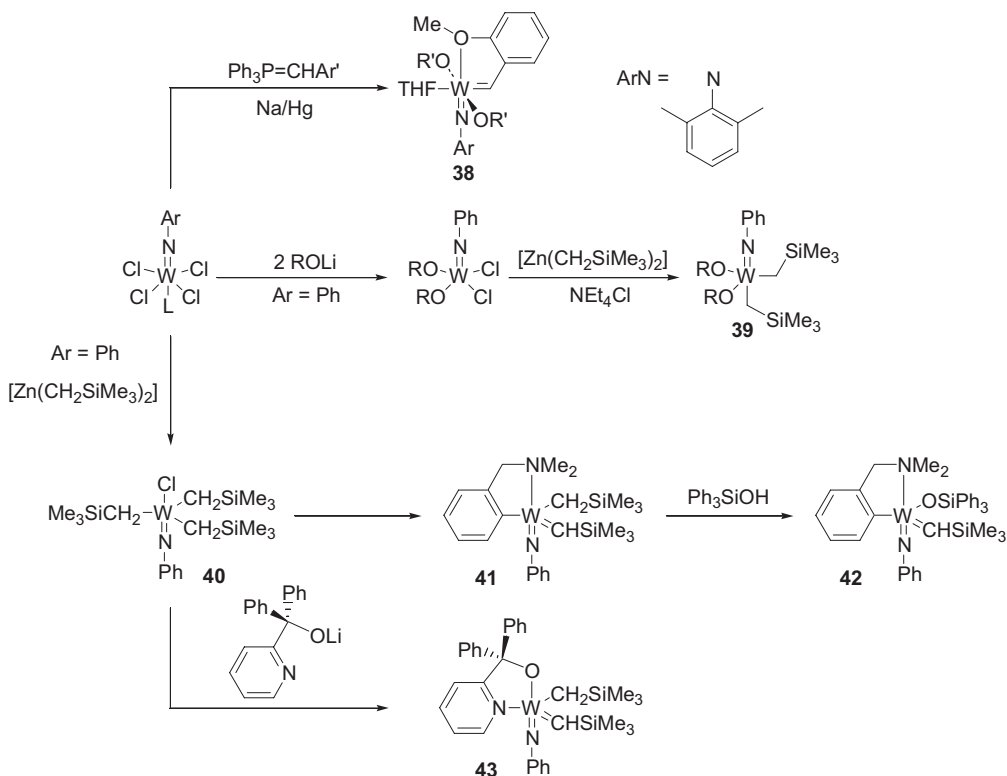


Scheme 1.4-12. Preparation of **31** (a: R = $t\text{Bu}$, b: R = $[(\text{CH}_3)_2(\text{CF}_3)\text{C}]$, c: R = $[(\text{CH}_3)(\text{CF}_3)_2\text{C}]$, d: R = $[(\text{CF}_3)_3\text{C}]$, e: R = OAr).

Scheme 1.4-13. Reactivity of **31**.Scheme 1.4-14. ROMP catalyzed by **31a**.

can readily be observed, and its reaction with 3-hexene gives the corresponding metallacyclobutane **36** at low temperatures, as evidenced by NMR spectroscopy.

While the corresponding parent alkoxide complex $[(t\text{BuO})_2\text{W}(=\text{CH}t\text{Bu})(=\text{NAr})]$ is rather unreactive towards acyclic olefins, it shows very good activity for more reactive monomers, such as strained cycloalkenes like norbornene, to give living polymers or block copolymers (Scheme 1.4-14) [26, 27]. A wide variety of alk-



Scheme 1.4-15. Other imidoalkylidene complexes.

oxide derivatives have been prepared, but the (*t*BuO) and the $[(\text{CF}_3)_2(\text{CH}_3)\text{CO}]$ ligands are more stable, and aryloxy systems are usually quite unreactive [28]. The substitution of the alkoxide moiety is also important; therefore when the methyl is replaced by a phenyl group, cyclometallation takes place to give a monoalkyl species (37) (Scheme 1.4-13). Noteworthy is the fact that 39, a bis(trimethylsilylmethyl) derivative, catalyzes the ROMP under photochemical conditions [29]. The high reactivity of these imido alkylidene complexes has led to the development of various analogous W alkylidene systems or some dialkyl precursors (38, 40–43; Scheme 1.4-15), but they display little to no activity in acyclic olefin metathesis and are restricted to the ROMP of strained cyclic olefins [30, 31].

1.4.7

Summary and Outlooks

Metallocarbene tungsten complexes exhibit fascinating properties in various aspects of the olefin metathesis reaction, including ring-opening polymerization, ring-closing metathesis, and cross-metathesis. Over the years, the design of well-defined metallocarbenes has afforded numerous efficient catalysts for the creation

of C=C bonds, which can be now used by organic and polymer chemists. For example, they can work with unfunctionalized, but also tolerate functionalized, olefins, dienes, or cycloolefins. Nonetheless, one of the weaknesses of the W family remains in its sensitivity to air and moisture and to some functional groups required by modern organic synthesis (such as the absence of protection-deprotection steps).

However, these complexes still have significant advantages over their ruthenium analogues in the sense that they can exhibit extremely high stereoselectivity (up to 99%), depending on their ligand environments. Stereochemical control is a crucial point in organic synthesis, and this point probably should be addressed more systematically. These complexes are good candidates for enantioselective synthesis via olefin metathesis, [32] as has been shown for their molybdenum analogues [33].

Another problem arises from deactivation and from the difficulty in separating them from the reaction mixture (typical for homogeneous catalysts). As demonstrated by Boncella, one route of deactivation is probably via dimerization of the highly reactive intermediates (such as $[W]=CH_2$), which could be prevented upon the isolation of active sites on a support.

References

- 1 a) M. LECONTE, J.-M. BASSET, *ChemTech* **1980**, 10, 762. b) F. QUIGNARD, C. LARROCHE, M. LECONTE, J.-M. BASSET, In *Mechanistic aspects of the olefin mechanism reaction* (Ed. Braterman), Plenum press, **1983**.
- c) K. J. IVIN, J. C. MOL, In *Olefin Metathesis and Metathesis Polymerization*, Academic Press, **1997**.
- 2 N. CALDERON, E. A. OFSTEAD, W. A. JUDY, *J. Polym. Sci.* **1967**, 5, 2209.
- 3 a) W. R. KROLL, G. DOYLE, *J. Chem. Soc., Chem. Commun.* **1971**, 839. b) C. P. CASEY, T. J. BURKHARDT, *J. Am. Chem. Soc.* **1973**, 95, 5833. c) T. J. KATZ, S. J. LEE, *Tetrahedron Lett.* **1976**, 4247.
- 4 a) R. R. SCHROCK, *J. Am. Chem. Soc.* **1974**, 96, 6796. b) J. FELDMAN, R. R. SCHROCK, *Progress in Inorg. Chem.* **1991**, 39, 2. c) R. R. SCHROCK, *Chem. Rev.* **2002**, 102, 145.
- 5 R. R. SCHROCK, *Polyhedron* **1995**, 14, 3177.
- 6 a) R. R. SCHROCK, S. ROCKLAGE, J. WENGROVIUS, G. RUPPRECHT, J. FELLMANN, *J. Mol. Cat.* **1980**, 8, 73. b) M. R. CHURCHILL, A. L. RHEINGOLD, W. J. YOUNG, R. R. SCHROCK, *J. Organomet. Chem.* **1981**, 204, C17. c) J. WENGROVIUS, R. R. SCHROCK, *Organometallics* **1982**, 1, 148.
- 7 J. H. WENGROVIUS, R. R. SCHROCK, M. R. CHURCHILL, J. R. MISSERT, W. J. YOUNG, *J. Am. Chem. Soc.* **1980**, 8, 4515.
- 8 M. B. O'DONOGHUE, R. R. SCHROCK, A. M. LAPOINTE, W. M. DAVIES, *Organometallics* **1996**, 15, 1334.
- 9 F. JAVIER DE LA MATA, R. H. GRUBBS, *Organometallics* **1996**, 15, 577.
- 10 O. FUJIMURA, F. JAVIER DE LA MATA, R. H. GRUBBS, *Organometallics* **1996**, 15, 186.
- 11 a) J. KRESS, M. WESOLEK, J. OSBORN, *J. Chem. Soc., Chem. Commun.* **1982**, 514. b) J. KRESS, J. OSBORN, *J. Am. Chem. Soc.* **1983**, 105, 6347.
- 12 J. KRESS, A. AGUERO, J. OSBORN, *J. Mol. Cat.* **1986**, 36, 1.
- 13 a) J. H. FREUNDENBERGER, R. R. SCHROCK, *Organometallics* **1985**, 4, 1937. b) J. A. HEPPERT, S. D. DIETZ, N. W. EILERTS, R. W. HENNING, M. D. MORTON, F. TAKUSAGAWA, F. A. KAUL, *Organometallics* **1992**, 12, 2565.
- 14 M. T. YOUINOU, J. KRESS, J. FISCHER, A. AGUERO, J. OSBORN, *J. Am. Chem. Soc.* **1988**, 110, 1488.
- 15 J. KRESS, J. OSBORN, *Angew. Chem. Int. Ed.* **1992**, 31, 1584.
- 16 F. QUIGNARD, M. LECONTE, J.-M. BASSET, L.-Y. HSU, J. J. ALEXANDER, S. G. SHORE, *Inorg. Chem.* **1987**, 26, 4272.

- 17 a) F. QUIGNARD, M. LECONTE, J.-M. BASSET, *J. Chem. Soc., Chem. Commun.* **1985**, 1816. F. QUIGNARD, M. LECONTE, J.-M. BASSET, *J. Mol. Cat.* **1986**, 36, 13. b) D. BOUTARFA, C. PAILLET, M. LECONTE, J.-M. BASSET, *J. Mol. Cat.* **1991**, 69, 157.
- 18 J.-L. COUTURIER, C. PAILLET, M. LECONTE, J.-M. BASSET, K. WEISS, *Angew. Chem. Int. Ed.* **1992**, 31, 628.
- 19 a) J.-L. COUTURIER, M. LECONTE, J.-M. BASSET, *J. Organometal. Chem.* **1993**, 451, C7. b) J.-L. COUTURIER, K. TANAKA, M. LECONTE, J.-M. BASSET, J. OLLIVIER, *Angew. Chem. Int. Ed.* **1993**, 32, 112. c) J.-L. COUTURIER, M. LECONTE, J.-M. BASSET, In *Transition Metal Carbyne Complexes*. **1993**, p 39. d) F. LEFEBVRE, M. LECONTE, S. PAGANO, A. MUTCH, J.-M. BASSET, J. OLLIVIER, *Polyhedron* **1995**, 14, 3209. e) M. LECONTE, I. JOURDAN, S. PAGANO, F. LEFEBVRE, J.-M. BASSET, *J. Chem. Soc., Chem. Commun.* **1995**, 857.
- 20 G. DESCOTES, J. RAMZA, J.-M. BASSET, S. PAGANO, *Tetrahedron Lett.* **1994**, 40, 7379.
- 21 a) D. D. VANDERLENDE, K. A. ABBOUD, J. M. BONCELLA, *Organometallics* **1994**, 13, 3378. b) W. M. VAUGHAN, K. A. ABBOUD, J. M. BONCELLA, *J. Am. Chem. Soc.* **1995**, 117, 11015. c) S.-Y. S. WANG, K. A. ABBOUD, J. M. BONCELLA, *J. Am. Chem. Soc.* **1997**, 119, 11990. d) S.-Y. S. WANG, D. D. VANDERLENDE, K. A. ABBOUD, J. M. BONCELLA, *Organometallics* **1998**, 17, 2628.
- 22 S. F. PEDERSEN, R. R. SCHROCK, *J. Am. Chem. Soc.* **1982**, 104, 7483.
- 23 a) C. J. SCHAVIERIEN, J. C. DEWAN, R. R. SCHROCK, *J. Am. Chem. Soc.* **1986**, 108, 2771. b) R. R. SCHROCK, R. DePUE, J. FELDMAN, C. J. SCHAVIERIEN, J. C. DEWAN, A. H. LIU, *J. Am. Chem. Soc.* **1988**, 110, 1423.
- 24 a) J. FELDMAN, W. M. DAVIES, R. R. SCHROCK, *Organometallics* **1989**, 8, 2266. b) J. FELDMAN, J. S. MURDZEK, W. M. DAVIES, R. R. SCHROCK, *Organometallics* **1989**, 8, 2260.
- 25 G. C. BAZAN, R. R. SCHROCK, M. B. O'REGAN, *Organometallics* **1991**, 10, 1062.
- 26 R. R. SCHROCK, *Acc. Chem. Res.* **1990**, 23, 158.
- 27 a) R. R. SCHROCK, J. FELDMAN, R. H. GRUBBS, L. CANNIZZO, *Macromolecules* **1987**, 20, 1169. b) R. R. SCHROCK, S. A. KROUSE, K. KNOLL, J. FELDMAN, J. S. MURDZEK, D. C. YANG, *J. Mol. Cat.* **1988**, 20, 243. c) K. KNOLL, S. A. KROUSE, R. R. SCHROCK, *J. Am. Chem. Soc.* **1988**, 110, 4424. d) S. A. KROUSE, R. R. SCHROCK, *Macromolecules* **1988**, 21, 1885. e) K. KNOLL, R. R. SCHROCK, *J. Am. Chem. Soc.* **1989**, 111, 7989. f) T. M. SWAGER, R. H. GRUBBS, *J. Am. Chem. Soc.* **1989**, 111, 4413. g) R. SCHLUND, R. R. SCHROCK, W. E. CROWE, *J. Am. Chem. Soc.* **1989**, 111, 8004.
- 28 R. R. SCHROCK, R. T. DePUE, J. FELDMAN, K. B. YAP, D. C. YANG, W. M. DAVIES, L. PARK, M. DiMARE, M. SCHOFIELD, J. ANHAUS, E. WALBORSKY, E. EVITT, C. KRÜGER, P. BETZ, *Organometallics* **1990**, 9, 2262.
- 29 P. A. VAN DER SCHAAP, A. HAFNER, A. MÜHLEBACH, *Angew. Chem. Int. Ed.* **1996**, 35, 1845.
- 30 a) L. K. JOHNSON, S. C. VIRGIL, R. H. GRUBBS, *J. Am. Chem. Soc.* **1990**, 112, 5384. b) L. K. JOHNSON, M. FREY, T. A. ULIBARRI, S. C. VIRGIL, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1993**, 115, 8167.
- 31 a) P. A. VAN DER SCHAAP, W. J. J. SMEETS, A. L. SPEK, G. VAN KOTEN, *J. Chem. Soc., Chem. Commun.*, **1992**, 717. b) P. A. VAN DER SCHAAP, R. A. T. M. ABBENHUIS, D. M. GROVE, W. J. J. SMEETS, A. L. SPEK, G. VAN KOTEN, *Organometallics* **1993**, 12, 3955. c) P. A. VAN DER SCHAAP, W. J. J. SMEETS, A. L. SPEK, G. VAN KOTEN, *J. Chem. Soc., Chem. Commun.*, **1993**, 504. d) P. A. VAN DER SCHAAP, R. A. T. M. ABBENHUIS, W. P. A. VAN DER NOORT, R. DE GRAAF, D. M. GROVE, W. J. J. SMEETS, A. L. SPEK, G. VAN KOTEN, *Organometallics* **1994**, 13, 1433.
- 32 W. C. P. TSANG, K. C. HULTZSCH, J. B. ALEXANDER, P. J. BONITATEBUS, R. R. SCHROCK, A. H. HOUEYDA, *J. Am. Chem. Soc.* **2003**, 125, 6337.
- 33 R. R. SCHROCK, A. H. HOUEYDA, *Chem. Eur. J.* **2001**, 7, 945.

1.5

Fischer Metal Carbenes and Olefin Metathesis

Thomas J. Katz

1.5.1

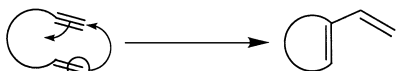
Fischer Metal Carbenes and Olefin Metathesis

It was the discovery of effective initiators that made olefin metathesis the useful transformation it is today. The initiators evolved in three stages [1]. The first initiators were those that led to the discovery of the transformation: mixtures of molybdenum oxide on alumina either with aluminum alkyls or aluminum hydrides plus hydrogen. The second were at first mixtures of WCl_6 or MoCl_5 , and later other transition metal derivatives, with organoaluminum and later with organotin compounds. In 1965, at about the same time these were discovered, RuCl_3 in ethanol was also found to be an initiator, but the importance of the discovery was not appreciated until Grubbs elaborated it some 25 years later [2]. The third initiators were pure isolable metal carbenes, unmixed with co-catalysts. Their development has recently been explosive and their application in fine chemical synthesis profuse. The reasons are that metal-carbene initiators provide a number of benefits: tolerance for functional groups, freedom from side-reactions, stereospecificity, control of polymer molecular weights, and rational initiator design. The first such initiators, used more than a quarter of a century ago, were the Fischer metal carbenes, and many of the basic principles governing olefin metatheses were discovered by their use.

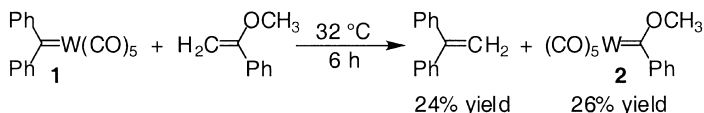
1.5.2

The Role of Fischer Metal Carbenes in Metathesis

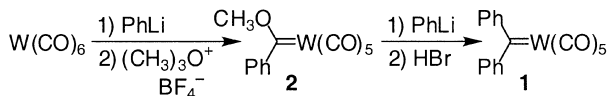
Metal carbenes are molecules that have metal-carbene bonds, and although the qualifier “Fischer” has been used in various ways, it is attached here to those metal carbenes that have carbonyl groups or other strong π -acceptors bonded to the metal atoms. Fischer metal carbenes were the first unadulterated metal carbenes found to initiate three of the fundamental transformations relating to the olefin metathesis reaction: (1) olefin metathesis itself [3–8], (2) the polymerization of acety-



Scheme 1.5-1. Rearrangement of an enyne to a diene.



Scheme 1.5-2. Methylene-tungsten carbonyl interchange.



Scheme 1.5-3. Synthesis of two Fischer metal carbenes.

lenes [9], and (3) the rearrangement of enynes to dienes (Scheme 1.5-1) [10]. Moreover, their use established some of the benefits pure metal-carbene initiators could provide [1, 11]. Stereospecificities could be achieved that were previously unattainable [5]. Lewis acid co-catalysts, previously thought to be required constituents of olefin metathesis initiators, could be eliminated [1]. And because deleterious acid-catalyzed reactions, such as polymerizations, are avoided, the metal-carbene initiators made it possible for the first time to initiate metatheses of trisubstituted alkenes [4, 7] and of 1,1-dialkylethylenes (in what is now called a degenerate metathesis) [3].

Fischer metal carbenes also played prominent roles in establishing the mechanism of the olefin metathesis reaction. They made it possible to demonstrate that metal carbenes can combine with alkenes to give different metal carbenes and different alkenes (Scheme 1.5-2), the key step in the mechanism of olefin metathesis [12]. They made it possible to determine the regiospecificity with which tungsten carbenes add to terminal olefins [13]. And they made it possible to verify the prediction [14] that isolable metal carbenes alone might initiate olefin metathesis reactions. This prediction was significant because it differentiated the hypothesis that metal carbenes propagate olefin metatheses [15] from previous mechanistic ideas, which envisioned the reaction proceeding through rings containing four carbon atoms [16].

The first Fischer metal carbene, also the first isolable metal carbene, which was made in 1964 (Scheme 1.5-3) by adding phenyllithium to tungsten hexacarbonyl [17]. The subsequent addition of trimethyloxonium fluoroborate produces (phenylmethoxycarbene)pentacarbonyltungsten (2) [18]. And, as Casey showed in 1973, when this metal carbene is combined with phenyllithium and then HBr, it gives (diphenylcarbene)pentacarbonyltungsten (1) [19]. In the 8 years following Fischer's discovery, some 300 metal carbenes were prepared [20], and it was therefore natural that they were used to test the mechanism of the olefin metathesis reaction.

Although this review omits work relating to novel transformations that occur when stoichiometric amounts of Fischer metal carbenes combine with acetylenes and alkenes [21], it summarizes experiments in which these metal carbenes were used in small amounts to initiate olefin metatheses and related reactions, and it shows some of the benefits metal-carbene initiators were found to provide.

1.5.3

Induction of Olefin Metatheses by Fischer Metal Carbenes

1.5.3.1

Properties of **2**

(Phenylmethoxycarbene)pentacarbonyltungsten (**2**) is a typical Fischer metal carbene. It is strikingly unreactive, stable in air, and must be heated to ca. 100 °C for reaction to occur [22]. Its C=W bond behaves in some ways like a C=O bond. Thus, nucleophiles attach to the carbene carbon, and donor atoms, such as O or N, on the carbene carbon diminish reactivity [19, 25]. Even some vinyl amines are sufficiently nucleophilic to combine with it at 100 °C, in a process related to Scheme 1.5-2 [26], and these amines [26], some vinyl ethers [27], and an *N*-vinyl amide [28] do the same with its chromium analogue. At 90–140 °C it also adds to α,β -unsaturated esters [29] and at, seemingly, 50 °C to ethyl vinyl ether under compressed CO [30], giving cyclopropanes [31]. But acyclic alkene hydrocarbons and unstrained cycloalkenes do not react [32] and, in particular, are not induced to undergo metathesis. Thus, no polyalkenamers [poly(1-alken-1, ω -diyl)s] are observed when cyclopentene, cycloheptene, or cyclooctene are warmed with 0.5 mol% of it for 7–26 days [33].

1.5.3.2

Olefin Metatheses Initiated by Metal Carbene **1**

There are, however, more reactive metal carbenes. Indeed, driving the synthesis of **1** (Scheme 1.5-3) was the idea, which proved correct, that **1** should be more reactive than **2** because it has a less electron-donating phenyl group in place of a methoxyl group [19]. Accordingly, when experiments were carried out to test whether metal carbenes alone would initiate olefin metatheses, (diphenylcarbene)-pentacarbonyltungsten (**1**) was the most reactive isolable metal carbene known. It, unlike (phenylmethoxycarbene)pentacarbonyltungsten (**2**), does initiate metatheses of a variety of alkenes, and with a number of benefits.

Some illustrations are in Table 1.5-1, which shows the results of experiments in which this metal carbene, in amounts less than or equal to 0.5 mol% and at temperatures of 40 °C or less, transformed a variety of cycloalkenes into their polyalkenamers (Scheme 1.5-4, R = H) [5]. One benefit of initiation by the metal carbene is also indicated in Table 1.5-1: the stereospecificities induced are exceptional. Essentially all the double bonds in the polyalkenamers have the less stable *cis*- (or

Tab. 1.5-1. Preparation and properties of polyalkenamers formed according to Scheme 1.5-4.^a

monomer	[olefin]/[W]	temp(°C)	time (h)	yield (%)	$\bar{M}_n \times 10^{-5}$	% cis	turnovers
cyclobutene	192	25	15	58	1.7	93	110
cyclopentene	500	37	14	40	1.2	86	200
cycloheptene	250	38	36	66	2.1	>98	165
cyclooctene	200	40	15	50	>2.0	97	100
norbornene	1680	25	18	91	3.3	92	1500

^aReprinted in abridged form from *Tetrahedron Letters* **1976**, T. J. Katz, S. J. Lee, and N. Acton, "Stereospecific Polymerizations of Cycloalkenes Induced by a Metal Carbene," pp. 4247–4250, Copyright 1976, with permission from Elsevier Science. The published IR and ¹³C NMR analyses of the fraction of double bonds that are *cis* are averaged in this table. For norbornene, the moles of olefin/moles of tungsten and the turnover number derive from the published data and correct a typographical error in the published table.

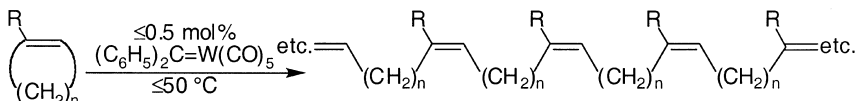
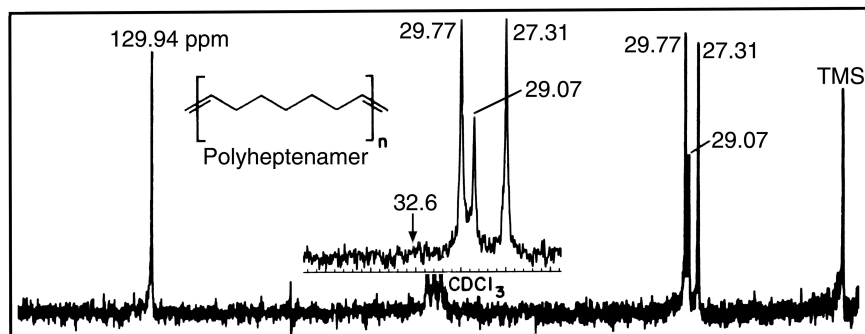
**Scheme 1.5-4.** Cycloalkene metathesis induced by **1**.

Fig. 1.5-1. ¹³C NMR spectrum (25 MHz) of a CDCl₃ solution of polyheptenamer, $\bar{M}_w = 1.4 \times 10^6$, $\bar{M}_n = 2.1 \times 10^5$, $[\eta]$ (30 °C, toluene) = 10.5 dl g⁻¹) made in 66% yield by combining 0.4 mol% of **1** with cycloheptene

in toluene at 38 °C for 36 h. The absence of a peak at 32.6 ppm (identified by an arrow), where material with *trans* double bonds would be observed, shows that the double bonds are $\geq 98\%$ *cis*.

Z-) stereochemistry, stereospecificity that is almost never achieved by any initiator [34–36] and has been achieved for a number of cycloalkenes only by this and a related metal-carbene preparation [5, 33]. That the double bonds are essentially all *cis* can be recognized in the polymers' ¹³C NMR spectra. An illustration is the spectrum of polyheptenamer in Figure 1.5-1, which differs greatly from the spectrum of a sample comprised of stereoisomeric units [35]. Similar stereospecificity is induced by metal carbene **1** in metatheses of acyclic alkenes. 2-Pentene that

was $96.0 \pm 0.4\%$ *cis* initially gave 1-butenes and 3-hexenes that were, respectively, $94.3 \pm 1\%$ and $92.5 \pm 1\%$ *cis* [8, 37]. Only two other initiators, also metal carbenes, achieve such high stereospecificity in this reaction [33, 34, 38].

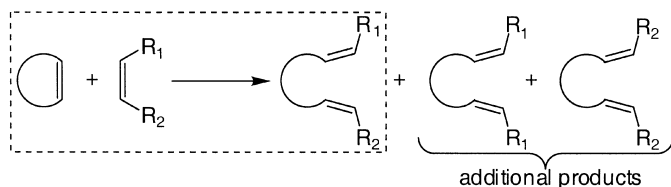
Other benefits of initiation by metal carbenes derive from the absence of Lewis acids. In their absence, it became possible to effect metatheses of trisubstituted alkenes. 1-Methylcyclobutene with WCl_6 plus EtAlCl_2 , and with many related initiators, gives polymers, but they are mainly saturated [4, 39], presumably because tertiary cations form in acid-catalyzed additions to the double bonds. But 3 mol% of metal carbene **1** at 50°C gives a 100% yield of the metathesis polymer 85% *Z*- (or *cis*-) polyisoprene (Scheme 1.5-4, $\text{R} = \text{CH}_3$, $n = 2$) [4]. Similarly, 1-methyl-*trans*-cyclooctene [7], 2-methylnorbornene [11], and 1-trimethylsilylcyclobutene [11], when combined with small amounts of **1**, give the corresponding metathesis polymers [40]. The importance of these polymers is not only that they form but also that their preparation made it possible in 1976 to test a hypothesis critical to the discovery of the mechanism of the olefin metathesis reaction. The significant point was that the monomers are linked in almost perfect – and in three of the cases, within the ca. 4% detectability limits of the analyses, perfect – head-to-tail order [4, 7, 11]. The polymers are translationally invariant.

1.5.3.3

Mechanistic Implications

The importance of these results relates to the first experiments that distinguished the metal-carbene mechanism from the then-prevailing hypotheses involving rings containing four carbons. The experiments found that the reactions of cycloalkenes with acyclic internal alkenes initially give two additional products for every one required by the four-carbon ring mechanisms (e.g., Scheme 1.5-5) [14, 15]. The problem was that the reactions of cycloalkenes with terminal alkenes seemed to fail the test: they do not give the additional products [15, 41]. For a number of years, this result could not be reconciled with the metal-carbene mechanism [16a–c, 41a,b] (even by Hérisson and Chauvin, who first proposed it [42]), and it was taken as evidence that the mechanism was incorrect [43].

The resolution of the problem is that during the metathesis of an alkene that is sufficiently unsymmetrical, one of the two metal carbenes derived by cleaving the double bond is present in much larger amounts than the other [1, 14, 44]. Accordingly, only it (or largely it) is the one that reacts, and only it (or largely it) is the one that forms. Consequently, Scheme 1.5-5 should give little or none of the addi-



Scheme 1.5-5. Metathesis of a cycloalkene with an acyclic alkene.

tional products [45]. Even though the metal-carbene mechanism is followed, only the products of the alternative, four-carbon ring mechanism are seen.

Another consequence is that because mainly (or only) one metal carbene of the two possible should propagate the metathesis of cyclic trisubstituted alkenes, the polymers of these cycloalkenes should be translationally invariant (Scheme 1.5-4). This was the result described above [4, 7, 11]. A third consequence is that, upon metathesis, terminal alkenes should largely be transformed into themselves, but with their terminal methylenes interchanged [1]. Isotopic labeling experiments show that this too is true [3, 41a], and Fischer metal carbenes proved essential for one of them. Since **1**, unlike the strongly Lewis acidic initiators, does not polymerize 1,1-disubstituted alkenes, its use made it possible to show that these alkenes' methylene groups exchange 1400 times faster with each other than with the disubstituted carbon fragments [3].

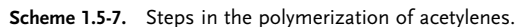
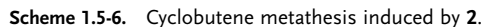
The three results described above (the absence of the additional products in Scheme 1.5-5, the translational invariance of the polymers from cycloalkenes, and the dominance of methylene exchange between terminal alkenes) would be observed whether the metal carbene that is more substituted predominates over the one that is less substituted or vice versa. An experiment carried out by Casey, Tuinstra, and Saemen distinguished which of the two prevails [13]. They showed that in reactions like those in Scheme 1.5-2 (in which the aryl group was *p*-tolyl instead of phenyl and in which a terminal hydrocarbon alkene took the place of the enol ether), the predominant alkene product was $\text{Ar}_2\text{C}=\text{CH}_2$. The implication is that the less-substituted metal carbene (the one with the $\text{CH}_2=\text{W}$ substructure) is the subordinate propagating metal carbene [41c]. The more-substituted metal carbene is dominant.

In these experiments, the metal-carbene products were not observed, but in other experiments based on Scheme 1.5-2, they were. Two were the reactions of **1** with the ethyl enol ethers of two ketones, cyclopentanone and norcamphor [46]. Others were the reactions of **1** (or better its chromium analogue, which also initiates ring-opening metathesis polymerization of an enol ether, dihydrofuran [47]) with carbohydrate-derived enol ethers [48]. Still others were the reactions of **2** with vinylamines (Section 1.5.3.1) and of a ruthenium carbene with ethyl vinyl ether and related sulfur and nitrogen compounds [49].

1.5.3.4

Metatheses Initiated by Metal Carbene **2**

In Section 1.5.3.1, metal carbene **2** was described as too unreactive to initiate metatheses of simple alkenes. But it is sufficiently reactive to initiate metatheses of alkenes that are strained. Thus, at 50 °C, 1 mole of **2** initiates the metathesis of 200 moles of cyclobutene, giving a 60% yield of 90% *cis* poly(but-2-ene-1,4-diyl), that is, perfect polybutadiene (Scheme 1.5-6) [6]. Other derivatives of cyclobutene react similarly [50], as do norbornene [6] and other derivatives of the metal carbene [11, 51]. One, with a triphenylphosphine group in place of one of the carbonyls in **2**, initiated the metathesis of 1.25 million times as many moles of norbornene, giving

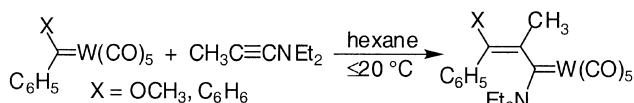


Metal-carbene **1** and relatives of **2** [52, 53], just as $(\text{Bu}_4\text{N}^+)_2 [\text{Mo}(\text{CO})_5]_2^-$ [54], $\text{Bu}_4\text{N}^+ \text{Mo}(\text{CO})_5\text{Cl}^-$ [55], and $(\text{OC})_5\text{W}-\text{NHEt}$ [53], when combined with Lewis acids give active initiators of olefin metatheses, including metatheses of such functionalized alkenes as pent-4-enyl acetate and methyl dec-9-enoate [52e,f]. Also pure tungsten carbynes, formed from Fischer carbenes and Lewis acids, initiate cycloolefin metatheses and, unlike the mixtures that contain excess Lewis acids [53], induce *cis* stereoselectivity almost as great as that achieved by pure **1** and **2** [56]. The reactive species have not been identified.

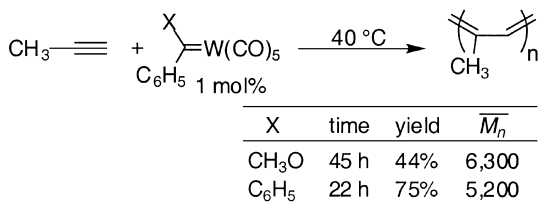
Initiation of Acetylene Polymerization by Fischer Metal Carbenes

Introduction

Scheme 1.5-4, when $n > 0$, represents the ring-opening metathesis of a cycloalkene to a polyalkenamer, but when $n = 0$, it represents the polymerization of an acetylene to a polyacetylene. Remarkably, the transformation takes place, just as written, whether $n > 0$ or $n = 0$. This agrees with the idea that acetylene polymerizations might be special cases of olefin metatheses and that the steps traversed are therefore like those in Scheme 1.5-7 [57]. The suggestion was first put forward by Masuda, who found that both WCl_6 and $MoCl_5$ initiate polymerizations of phenylacetylene [58]. Evidence for the hypothesis is the observation that when polymerized in toluene by $MoCl_5$ plus $(C_6H_5)_4Sn$, phenylacetylene that has two ^{13}C atoms separated by a triple bond gives poly(phenylacetylene) that has these atoms separated by single bonds. The same phenylacetylene, when polymerized by $Ti(OBu)_4$ plus Et_3Al , gives poly(phenylacetylene) that has ^{13}C atoms separated by double bonds [59]. Other evidence for the hypothesis is the observation that Fischer metal carbenes combine as illustrated in Scheme 1.5-8 with acetylenes that have electron-donating groups attached to their triple bonds [60]. There are



Scheme 1.5-8. Insertion of an acetylene into a metal-carbene bond.



Scheme 1.5-9. Propyne polymerization induced by **1** and **2**.

numerous examples, including the following variations of Scheme 1.5-8: X is H [61] or SR [62]; the NEt₂ is replaced by OEt and the CH₃ by H [61, 63]; the W is replaced by Cr, Mo, or Mn [64]; and the phenyl group is replaced by other carbon residues [60, 62b, 64].

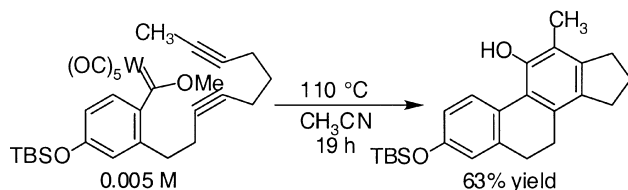
1.5.4.2

Examples of Acetylene Polymerizations Initiated by Fischer Metal Carbenes

In 1980 it was found, as illustrated in Scheme 1.5-9, that the polymerizations of a number of acetylenes, including propyne, phenylacetylene, 1-hexyne, and *tert*-butylacetylene, could be induced by Fischer metal carbenes **1** and **2** [9, 65]. There were a number of benefits. The yields were good (for poly(*tert*-butylacetylene) many times the best previously recorded), and the purities of the polymers, as evidenced by their ¹H and ¹³C NMR spectra, were very high [9].

Acetylene polymerizations have also been induced by **2** promoted by light [66] and by a dinuclear tungsten-carbonyl derivative of 3,3-dimethylpropylidene [67]. A Fischer carbyne, C₆H₅C≡W(CO)₄Br, also induces polymerizations of acetylenes, including terminal acetylenes RC≡CH, where R = Me, Bu, *t*-Bu, Ph, but, more interestingly, disubstituted acetylenes and acetylene itself, and most interestingly, functionalized acetylenes RC≡CC(CH₂)₃X, where X = Cl, CN, and CO₂CH₃ [56]. These last were the first polymerizations ever effected of functionalized acetylenes other than derivatives of propiolic acid or propargyl alcohol [68].

Related to the acetylene polymerization are a multitude of transformations in which stoichiometric amounts of Fischer metal carbenes add to acetylenes and other reactions ensue [21]. Although the Dötz reaction is best known and was discovered the earliest, Scheme 1.5-10 is presented [69] because it illustrates successive additions to acetylenes and because it uses a carbene of tungsten, a more common component of olefin metathesis initiators than chromium, the characteristic metal of the Dötz reaction [70]. Other reactions that similarly stitch together two acetylenes take place faster and at convenient, higher concentrations when the reagents are metal carbynes rather than metal carbenes [71]. Their effec-



Scheme 1.5-10. Tandem insertion of acetylenes and CO into a metal-carbene bond.

tiveness in both these reactions and acetylene polymerizations has been attributed speculatively to metal carbynes $\text{RC}\equiv\text{M}(\text{CO})_4\text{Br}$ transforming into metal carbenes $\text{R}(\text{Br})\text{C}=\text{M}(\text{CO})_4$ [56]. Other reactions initiated by additions of metal carbenes to acetylenes are considered in the next section.

1.5.5

Actuation of Olefin Metathesis by Acetylenes

1.5.5.1

Metatheses of Cyclic and Acyclic Alkenes Actuated by An Acetylene

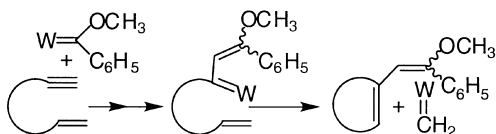
Scheme 1.5-7 shows that when alkoxy-substituted Fischer metal carbenes such as **2** add to acetylenes, the alkoxy groups separate from the carbene centers, and the more so the more acetylenes are subsequently added. Since, as seen in Section 1.5.3.1, alkoxy groups stabilize metal carbenes, their removal should activate alkoxy-substituted metal carbenes to launch into otherwise unachievable processes, including olefin metatheses. Indeed, the addition of small amounts of phenylacetylene activates (phenylmethoxycarbene)pentacarbonyltungsten (**2**), which in its absence is ineffective (Section 1.5.3.1), to initiate metatheses of unstrained cycloalkenes, such as cycloheptene and cyclooctene, and of acyclic alkenes, such as *cis*-2-pentene [33]. The stereospecificities of these metatheses, like those induced by (diphenylcarbene)pentacarbonyltungsten (**1**), are very high [72]. The double bonds formed are $\geq 94\%$ *cis*. Phenylacetylene similarly actuates other reagents that initiate its polymerization (such as WCl_6) to effect olefin metatheses [73].

Because the reactivities of double- and triple bonds toward conjugatively unstabilized and conjugatively stabilized metal carbenes differ [74], an optimal amount of phenylacetylene is required to achieve actuation. If the amount is too large, the acetylene inhibits the olefin metatheses it otherwise would induce [33, 73].

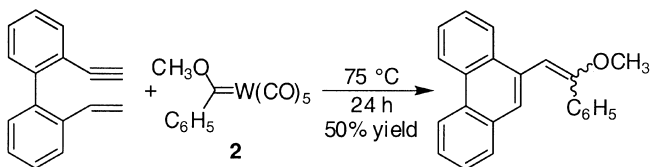
1.5.5.2

Reaction of Enynes With Fischer Metal Carbenes

Consider the reverse of the above. Suppose the amount of the olefin were sufficiently large to quench the acetylene polymerization after only a single cycle.



Scheme 1.5-11. Acetylene polymerization quenched by an alkene immediately after initiation.



Scheme 1.5-12. Transformation of an enyne into a diene.

Envisioned as achieved by binding the olefin to the acetylene, the idea is summarized in abbreviated form in Scheme 1.5-11. One of the first examples is summarized in Scheme 1.5-12 [10]. Among the more recent examples [75] is the analogous reaction of (*E*-PhCH=CHCH₂)(HC≡CCH₂)NTs with 1.2 equivalents of (phenylethoxycarbene)pentacarbonylchromium at 70 °C, which, after hydrolysis, gives a 69% yield of a dihydropyrrolylacetophenone [76].

1.5.5.3

Rearrangement of Enynes to Dienes

Scheme 1.5-12 implies that the metal carbene CH₂=W formed in Scheme 1.5-11 competes unsuccessfully with the reagent methoxycarbene (**2**) for reaction with the starting enyne, probably because the former metal carbene decomposes before substantial concentrations can accumulate. However, if the amounts of **2** are greatly reduced, the methylene carbene does compete successfully [10]. The reagent **2** acts only as an initiator and the alkene as a chain-transfer agent. After **2** initiates reaction, the CH₂=W produced in Scheme 1.5-11 takes over the former's role. It adds to the enyne, forming a diene and reforming CH₂=W. The cycle then repeats. Accordingly, the overall transformation is the fantastic one in Scheme 1.5-1. The fact is that this transformation can be brought about by combining the enyne with 0.01 of an equivalent of either **1** at 50 °C or **2** at 75 °C, and it takes place similarly when the CH₂ group is replaced by a (CH₃)₂C group or by a (CH₃)(H)C group [10]. The stereochemistry of the diene formed in this last example shows what the stereochemistry is of the electrocyclic transformation that converts a metallacyclobutene into a metalladiene. Since the double bond external to the ring in the product is 95% *cis* (the initiator was **1**), the electrocyclic reaction rotates the methyl group in the direction that places it *cis* to the metal carbene. The stereoselection is the same as that giving rise to the Dötz reaction, but it occurs in the absence of the alkoxy group that has been suggested to be the root of that reaction's stereoselection [77].

Although Fischer metal carbenes (and also MoCl_5 plus Ph_4Sn) initiate the enyne rearrangements described above and others [75, 78, 79], ruthenium carbenes, as Grubbs recently showed, do so more effectively [80, 81]. Accordingly, the application of these rearrangements in organic syntheses may just be beginning to be explored [75, 82].

References

- 1 For a brief summary, see T. J. KATZ, *Adv. Organomet. Chem.* **1977**, 16, 283.
- 2 (a) S. T. NGUYEN, L. K. JOHNSON, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1992**, 114, 3974. (b) P. SCHWAB, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1996**, 118, 100. (c) M. SCHOLL, S. DING, C. W. LEE, R. H. GRUBBS, *Org. Lett.* **1999**, 1, 953.
- 3 J. MCGINNIS, T. J. KATZ, S. HURWITZ, *J. Am. Chem. Soc.* **1976**, 98, 605.
- 4 T. J. KATZ, J. MCGINNIS, C. ALTUS, *J. Am. Chem. Soc.* **1976**, 98, 606.
- 5 T. J. KATZ, S. J. LEE, N. ACTON, *Tetrahedron Lett.* **1976**, 4247.
- 6 T. J. KATZ, N. ACTON, *Tetrahedron Lett.* **1976**, 4251.
- 7 S. J. LEE, J. MCGINNIS, T. J. KATZ, *J. Am. Chem. Soc.* **1976**, 98, 7818.
- 8 T. J. KATZ, W. H. HERSH, *Tetrahedron Lett.* **1977**, 585.
- 9 T. J. KATZ, S. J. LEE, *J. Am. Chem. Soc.* **1980**, 102, 422.
- 10 T. J. KATZ, T. M. SIVAVEC, *J. Am. Chem. Soc.* **1985**, 107, 737.
- 11 T. J. KATZ, S. J. LEE, M. A. SHIPPEY, *J. Mol. Catal.* **1980**, 8, 219.
- 12 C. P. CASEY, T. J. BURKHARDT, *J. Am. Chem. Soc.* **1974**, 96, 7808.
- 13 C. P. CASEY, H. E. TUINSTR, M. C. SAEMAN, *J. Am. Chem. Soc.* **1976**, 98, 608.
- 14 T. J. KATZ, J. MCGINNIS, *J. Am. Chem. Soc.* **1975**, 97, 1592.
- 15 J. L. HÉRISSON, Y. CHAUVIN, *Makromol. Chem.* **1970**, 141, 161.
- 16 (a) N. CALDERON, The Olefin Metathesis Reaction, Chapter 10 in *Chemistry of Double-Bonded Functional Groups, Part 2*; S. PATAI (Ed.), Wiley, USA, **1977**. (b) J. C. MOL, J. A. MOULIJN, *Advan. Catal.* **1975**, 24, 131. (c) W. B. HUGHES, *Organomet. Chem. Synth.* **1972**, 1, 341. (d) J. LEVISALLES, H. RUDLER, D. VILLEMIN, *J. Organomet. Chem.* **1975**, 87, C7. (e) J. BASSET, G. COUDURIER, R. MUTIN, H. PRALIAUD, Y. TRAMBOUZE, *J. Catal.* **1974**, 34, 196. (f) C. G. BIEFELD, H. A. EICK, R. H. GRUBBS, *Inorg. Chem.* **1973**, 12, 2166.
- 17 E. O. FISCHER, A. MAASBÖL, *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 580.
- 18 E. O. FISCHER, U. SCHUBERT, W. KLEINE, H. FISCHER, *Inorg. Synth.* **1979**, 19, 165.
- 19 (a) C. P. CASEY, T. J. BURKHARDT, *J. Am. Chem. Soc.* **1973**, 95, 5833. (b) C. P. CASEY, T. J. BURKHARDT, C. A. BUNNELL, J. C. CALABRESE, *J. Am. Chem. Soc.* **1977**, 99, 2127.
- 20 D. J. CARDIN, B. CETINKAYA, M. F. LAPPERT, *Chem. Rev.* **1972**, 72, 575.
- 21 (a) W. D. WULFF, Chapter 5.3, Vol 12 in *Comprehensive Organometallic Chemistry II*; E. W. ABEL, F. G. A. STONE, G. WILKINSON, Eds.; Pergamon Press, USA, **1995**. (b) D. F. HARVEY, D. M. SIGANO, *Chem. Rev.* **1996**, 96, 271. (c) F. ZARAGOZA DÖRWALD, *Metal Carbenes in Organic Synthesis*, Wiley-VCH, USA, **1999**. (d) J. W. HERNDON, *Coord. Chem. Rev.* **2000**, 206–207, 237. (e) A. FÜRSTNER, *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 3013. (f) A. FÜRSTNER (Ed.), *Alkene Metathesis in Organic Synthesis*, Springer, USA, **1998**. (g) T. J. KATZ, G. X.-Q. YANG, B. H. RICKMAN, T. IWASHITA, *J. Am. Chem. Soc.* **1993**, 115, 2038, and references therein.
- 22 The reaction of **2** with methyl acrylate required heating to 100 °C for 6 h [23]. The chromium analogue was heated at 135 °C for 12 h to achieve its decomposition [24a], and with methyl acrylate it was found to react much less slowly than the

- tungsten derivative (2) [23]. The methyl(methoxy)carbene-chromium analogue requires 3 h at 160 °C to decompose [24b].
- 23 A. WIENAND, H.-U. REISSIG, *Organometallics* **1990**, 9, 3133.
 - 24 (a) E. O. FISCHER, B. HECKEL, K. H. DÖTZ, J. MÜLLER, H. WERNER, J. *Organometal. Chem.* **1969**, 16, P29.
(b) E. O. FISCHER, D. PLABST, *Chem. Ber.* **1974**, 107, 3326.
 - 25 C. F. BERNASCONI, *Chem. Soc. Rev.* **1997**, 26, 299.
 - 26 J. BARLUENGA, F. AZNAR, A. MARTIN, *Organometallics* **1995**, 14, 1429.
 - 27 (a) E. O. FISCHER, K. H. DÖTZ, *Chem. Ber.* **1972**, 105, 3966. (b) M. HOFFMANN, M. BUCHERT, H.-U. REISSIG, *Chem. Eur. J.* **1999**, 5, 876.
 - 28 E. O. FISCHER, B. DORRER, *Chem. Ber.* **1974**, 107, 1156.
 - 29 K. H. DÖTZ, E. O. FISCHER, *Chem. Ber.* **1972**, 105, 1356.
 - 30 E. O. FISCHER, K. H. DÖTZ, *Chem. Ber.* **1972**, 105, 3966. (The temperature and pressure were not specified.)
 - 31 M. BROOKHART, W. B. STUDABAKER, *Chem. Rev.* **1987**, 87, 411.
 - 32 Attempts to add its chromium analogue to tetramethylethylene [24a] or the methyl(methoxy)carbene-chromium analogue to cyclohexene [E. O. FISCHER, A. MAASBÖL, J. *Organometal. Chem.* **1968**, 12, P15] failed.
 - 33 T. J. KATZ, S. J. LEE, M. NAIR, E. B. SAVAGE, *J. Am. Chem. Soc.* **1980**, 102, 7940.
 - 34 K. J. IVIN, J. C. MOL, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, USA, **1997**.
 - 35 P. DOUNIS, W. J. FEAST, A. M. KENWRIGHT, *Polymer* **1995**, 36, 2787.
 - 36 The double bonds are largely *trans* in the polymers formed from cyclopent-, -hept, and -octenes (as well as other cycloolefins) and four initiators of general structure $M(=CHtBu)(OR)_2(NAr)$, $M = Mo, W$, [35]. They are *trans* in the polynorbornenamer formed by Grubbs' $Ru=CHCH=CPh_2$ -initiator or by $RuCl_3$ (see footnote 16 in reference [2a]).
 - 37 T. J. KATZ, W. H. HERSH, *Tetrahedron Lett.* **1977**, 585.
 - 38 J.-L. COUTURIER, C. PAILLET, M. LECONTE, J.-M. BASSET, K. WEISS, *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 628.
 - 39 G. DALL'ASTA, R. MANETTI, *Atti Accad. Naz. Lincei, Rend., Cl. Sci. Fis. Mat. Nat.* **1966**, 41, 351.
 - 40 The double bonds in the first are $76 \pm 1\%$ *E* (*trans*), in the second comparably *Z*- and *E*-, and in the third $>98\%$ *E* (*cis*).
 - 41 (a) W. J. KELLY, N. CALDERON, J. *Macromol. Sci. Chem.* **1975**, A9, 911.
(b) J. LAL, R. R. SMITH, *J. Org. Chem.* **1975**, 40, 775. (c) L. BENCZE, K. J. IVIN, J. J. ROONEY, *Chem. Commun.* **1980**, 834.
 - 42 From page 173 of Reference [15]: "On the contrary, this simple representation does not allow an interpretation of ... the observed distribution in the coreaction of cyclic olefins and α -olefins ..."
 - 43 Quoting from page 166 of Reference [16b]: "... This is not consistent with the scheme of Hérisson and Chauvin. However, with the scheme of Calderon, this can be explained. ... It may be concluded that ... the scheme of Calderon is to be preferred to that of Hérisson and Chauvin."
 - 44 T. J. KATZ, J. MCGINNIS, *J. Am. Chem. Soc.* **1977**, 99, 1903.
 - 45 It also means [1, 14, 44] that the metathesis of a cyclic with an acyclic olefin might give a 1:2:1 ratio of products at thermodynamic equilibrium, but not *initially*, as has been stated [15].
 - 46 (a) J. LEVISALLES, H. RUDLER, D. VILLEMEN, *J. Organomet. Chem.* **1978**, 146, 259. (b) J. LEVISALLES, H. RUDLER, D. VILLEMEN, J. DARAN, Y. JEANNIN, AND L. MARTIN, *J. Organomet. Chem.* **1978**, 155, C1. (c) H. RUDLER, *J. Mol. Catal.* **1980**, 8, 53.
 - 47 C. T. THU, T. BASTELBERGER, H. HÖCKER, *Macromol. Chem., Rapid Commun.* **1981**, 2, 383.
 - 48 W.-C. HAASE, M. NIEGER, K. H. DÖTZ, *Chem. Eur. J.* **1999**, 5, 2014.
 - 49 J. LOUIE, R. H. GRUBBS, *Organometallics* **2002**, 21, 2153.

- 50 C. T. THU, T. BASTELBERGER, H. HÖCKER, *Macromol. Chem., Rapid Commun.* **1981**, 2, 7.
- 51 M. DOHERTY, A. SIOVE, A. PARLIER, H. RUDLER, AND M. FONTANILLE, *Makromol. Chem. Macromol. Symp.* **1986**, 6, 33.
- 52 (a) W. R. KROLL, G. DOYLE, *Chem. Commun.* **1971**, 839. (b) E. O. FISCHER, W. R. WAGNER, *J. Organomet. Chem.* **1976**, 116, C21. (c) S. P. KOLESNIKOV, N. I. POVAROVA, A. YA. SHTEIN-SHNEIDER, O. M. NEFEDOV, *Bull. Acad. Sci. USSR* **1979**, 28, 2224. (d) D. S. BANASIAK, *U. S. Pat.* 4,248,738 (Feb. 3, 1981). (e) D. S. BANASIAK, *U. S. Pat.* 4,248,780 (May 26, 1981). (f) D. S. BANASIAK, *J. Mol. Catal.* **1985**, 28, 107. (g) I. LEYMET, A. SIOVE, A. PARLIER, H. RUDLER, M. FONTANILLE, *Makromol. Chem.* **1989**, 190, 2397.
- 53 Y. CHAUVIN, D. COMMEREUC, D. CRUYPELINCK, *Makromol. Chem.* **1976**, 177, 2637.
- 54 W. R. KROLL, G. DOYLE, *J. Catal.* **1972**, 24, 356.
- 55 G. DOYLE, *J. Catal.* **1973**, 30, 118.
- 56 T. J. KATZ, T. H. HO, N.-Y. SHIH, Y.-C. YING, V. I. W. STUART, *J. Am. Chem. Soc.* **1984**, 106, 2659.
- 57 The equations would be modified slightly if the cyclobutene is bypassed, as suggested by P. HOFMANN, M. HÄMMERLE, G. UNFRIED, *New J. Chem.* **1991**, 15, 769.
- 58 T. MASUDA, N. SASAKI, T. HIGASHIMURA, *Macromolecules* **1975**, 8, 717.
- 59 T. J. KATZ, S. M. HACKER, R. D. KENDRICK, C. S. YANNONI, *J. Am. Chem. Soc.* **1985**, 107, 2182.
- 60 K. H. DÖTZ, *Chem. Ber.* **1977**, 110, 78.
- 61 C. P. CASEY, S. W. POLICHNOWSKI, A. J. SHUSTERMAN, C. R. JONES, *J. Am. Chem. Soc.* **1979**, 101, 7282.
- 62 (a) R. AUMANN, J. SCHRÖDER, H. HEINEN, *Chem. Ber.* **1990**, 123, 1369. (b) K. H. DÖTZ, V. LEUE, *J. Organomet. Chem.* **1991**, 407, 337.
- 63 R. AUMANN, P. HINTERDING, *Chem. Ber.* **1991**, 124, 213.
- 64 K. H. DÖTZ, I. PRUSKIL, *Chem. Ber.* **1978**, 111, 2059, and references therein.
- 65 R. NOMURA, K. WATANABE, T. MASUDA, *Polym. Bull.* **1999**, 43, 177.
- 66 H. C. FOLEY, L. M. STRUBINGER, T. S. TARGOS, G. L. GEOFFROY, *J. Am. Chem. Soc.* **1983**, 105, 3064.
- 67 (a) J. LEVISALLES, F. ROSE-MUNCH, H. RUDLER, J.-C. DARAN, Y. DROMZEE, Y. JEANNIN, D. ADES, M. FONTANILLE, *Chem. Commun.* **1981**, 1055. (b) D. MEZIANE, A. SOUM, M. FONTANILLE, *Makromol. Chem.* **1985**, 186, 367, and **1988**, 189, 1407.
- 68 See footnote 21 in reference [56].
- 69 J. BAO, W. D. WULFF, V. DRAGISICH, S. WENGLOWSKY, R. G. BALL, *J. Am. Chem. Soc.* **1994**, 116, 7616.
- 70 For possible reasons the different metals bring about different reactions, see: (a) Reference [66]; (b) W. D. WULFF, B. M. BAX, T. A. BRANDVOLD, K. S. CHAN, A. M. GILBERT, R. P. HSUNG, J. MITCHELL, J. CLARDY, *Organometallics* **1994**, 13, 102; and (c) T. R. HOYE, J. A. SURIANO, *Organometallics* **1992**, 11, 2044.
- 71 T. M. SIVAVEC, T. J. KATZ, *Tetrahedron Lett.* **1985**, 26, 2159.
- 72 A ¹³C NMR spectrum to compare with Figure 1.5-1 is in [11].
- 73 T. J. KATZ, C.-C. HAN, *Organometallics* **1982**, 1, 1093.
- 74 (a) C.-C. HAN, T. J. KATZ, *Organometallics* **1985**, 4, 2186. (b) T. J. KATZ, E. R. SAVAGE, S. J. LEE, M. NAIR, *J. Am. Chem. Soc.* **1980**, 102, 7942.
- 75 M. MORI, in *Alkene Metathesis in Organic Synthesis*, A. FÜRSTNER (Ed), Springer, USA, **1998**, p 133 ff.
- 76 S. WATANUKI, N. OCHIFUJI, M. MORI, *Organometallics* **1995**, 14, 5062.
- 77 M. L. WATERS, T. A. BRANDVOLD, L. ISAACS, W. D. WULFF, A. L. RHEINGOLD, *Organometallics* **1998**, 17, 4298.
- 78 T. J. KATZ, in U. SCHUBERT (Ed.), *Advances in Metal Carbene Chemistry*, Reidel, Holland, **1989**, p. 293 ff.
- 79 (a) T. R. HOYE, J. A. SURIANO, *Organometallics* **1992**, 11, 2044. (b) S. WATANUKI, M. MORI, *Organometallics* **1995**, 14, 5054.
- 80 (a) S.-H. KIM, N. B. BOWDEN, R. H. GRUBBS, *J. Am. Chem. Soc.* **1994**, 116, 10801. (b) S.-H. KIM, W. J. ZUERCHER,

- N. B. BOWDEN, R. H. GRUBBS, *J. Org. Chem.* **1996**, *61*, 1073.
- 81** So does $[\text{RuCl}_2(\text{CO})_3]_2$: N. CHATANI, T. MORIMOTO, T. MUTO, S. MURAI, *J. Am. Chem. Soc.* **1994**, *116*, 6049.
- 82** (a) R. STRAGIES, U. VOIGTMANN, S. BLECHERT, *Tetrahedron Lett.* **2000**, *41*, 5465, and references therein. (b) T. R. HOYE, S. M. DONALDSON, T. J. VOS, *Org. Lett.* **1999**, *1*, 277. (c) M. MORI, T. KITAMURA, Y. SATO, *Synthesis* **2001**, 654. (d) N. SAITO, Y. SATO, M. MORI, *Org. Lett.* **2002**, *4*, 803. (e) M. E. LAYTON, C. A. MORALES, M. D. SHAIR, *J. Am. Chem. Soc.* **2002**, *124*, 773.

1.6

The Discovery and Development of Well-Defined, Ruthenium-Based Olefin Metathesis Catalysts

SonBinh T. Nguyen and Tina M. Trnka

A dream of many chemists is to see their work become useful to others during their lifetimes. There is no doubt that this dream has been realized in the case of the Grubbs ruthenium-based olefin metathesis catalysts, as the development of this chemistry and its applications over the last ten years has been breathtaking. Since the discovery of the first metathesis-active ruthenium alkylidene complex in 1992 [1] to date, this simple yet powerful class of compounds has become an indispensable tool in areas ranging from organic and polymer synthesis to materials and surface science. The authors are fortunate to have been directly involved in the development of these catalysts and to have witnessed the growth of their applications. This chapter aims to introduce the discovery and evolution of these catalysts over the last decade.

1.6.1

The Discovery of Well-Defined Ruthenium Olefin Metathesis Catalysts: A Personal Account by SonBinh Nguyen

The title of this chapter begins with the words “The Discovery,” which suggests a historical perspective. This context is especially pertinent to the Grubbs ruthenium olefin metathesis catalysts, and thus I ask for the reader’s indulgence while I describe the circumstances that led to the discovery of these compounds.

My first encounter with the field of olefin metathesis and with Professor Robert (Bob) Grubbs was at the end of 1989 when I was applying to graduate school. I called my mentor, Dr. Henry Bryndza at DuPont, to ask for his opinion, and it happened that Bob was visiting him. Henry convinced Bob to take a chance on accepting me into the graduate program at Caltech, and after visiting the school, I decided to attend and work for Bob on olefin metathesis chemistry. In the meantime, I worked at DuPont during the summer of 1990 as an intern. My project required me to synthesize all of the major Schrock tungsten-, molybdenum-, and rhenium-based olefin metathesis catalysts. The synthetic schemes published by Schrock and coworkers are elegant and require much skill from the practitioners

[2]. Beginning from the most basic starting materials, it took me about two to three weeks to make each type of catalyst in the *tert*-butoxide, trifluoro-*tert*-butoxide, and hexafluoro-*tert*-butoxide forms. I found that the tungsten derivatives, although crystalline, are the most sensitive to handle. The rhenium catalysts are the most tolerant but must be kept in solution, which is inconvenient. The molybdenum catalysts have just the right combination of crystallinity and tolerance to make them the best materials to handle. Nevertheless, the synthetic routes to these catalysts are lengthy because they involve α -hydrogen abstraction and anionic ligand substitution as two main steps. (I should note that the synthesis of the tungsten catalyst was shortened significantly that year by Johnson and Grubbs with ylid transfer chemistry [3, 4] and again two years later using cyclopropene methodology [5, 6]). In addition, I found that the potentially most disappointing step is invariably the final recrystallization, so one has to work with large amounts of material to obtain good yields. It also is critical to rigorously purify all materials at every step because a variety of impurities decrease the reaction yields.

The intrinsic oxophilicity and functional group reactivity of these catalysts, as well as my encounter with Bob earlier that year, placed the seed of an idea in my mind – that it would be wonderful to have an olefin metathesis catalyst that could be made easily, does not react with Lewis bases, and tolerates a wide range of functional groups. At this time, the Novak–Grubbs aqueous ruthenium-catalyzed ring-opening metathesis polymerization (ROMP) chemistry and its clever application in poly(ionophore) synthesis was almost two years old [7, 8]. Although it previously had been established that ruthenium-based olefin metathesis catalysts can tolerate the presence of protic species [9], the Novak–Grubbs papers had the effect of rekindling interests in late transition metal chemistry among members of the olefin metathesis community.

1.6.1.1

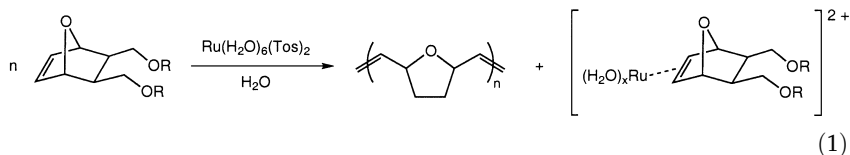
(PPh₃)₂Cl₂Ru=CH–CH=CPh₂, the First Well-Defined, Metathesis-Active Ruthenium Alkylidene Complex

The summer of 1990 ended and I went to Caltech for graduate school. After working on a variety of projects, Bob wisely steered me back to organometallic chemistry to work on the problem of finding a metathesis-active, well-defined ruthenium alkylidene complex. I was not the first person in the Grubbs group assigned this task, and I benefited greatly from previous attempts. The guidelines were to look for a Ru(II) alkylidene moiety that was not as nucleophilic as the alkylidenes in Schrock-type complexes, and combine it with a 16-electron metal center and at least one empty coordination site for olefin binding. At that time, the Roper halogenated ruthenium carbenes (see Chapter 1.7) most closely matched these criteria, but these promising candidates ultimately did not exhibit any olefin metathesis activity. However, this observation was useful because it suggested that we investigate metal carbenes with substituents other than halogens.

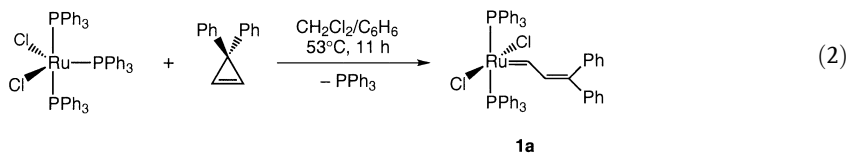
On another project, Lynda Johnson and Grubbs developed a general method for the synthesis of W(VI) vinylalkylidene complexes of the form (ArN)L₂Cl₂W=CH–

$\text{CH}=\text{CPh}_2$ (L = phosphine or phosphite) by the addition of 3,3-disubstituted cyclopropenes to reduced W(IV) precursors [5, 6]. In certain cases, they also isolated W(IV) –olefin complexes as the initial products from the reactions of the W(IV) precursors, $(\text{ArN})\text{WCl}_2\text{L}_3$, with the cyclopropenes. These olefin complexes then could be induced to rearrange to W(VI) vinylalkylidenes by a number of methods. It is interesting to note that this chemistry was facilitated initially because Lynda had access to samples of 3,3-disubstituted cyclopropenes made by Jeffrey Moore and Eric Ginsburg for another project.

Around the same time, the Grubbs group was actively pursuing the Novak–Grubbs discovery [7, 8] and screening ruthenium complexes for olefin metathesis activity [10–13]. This work revealed that the coordinatively labile Ludi complex, $\text{Ru}(\text{H}_2\text{O})_6(\text{Tos})_2$ [14, 15], was among the best olefin metathesis initiators. Further studies showed that the active ruthenium species in this system are generated from the reaction of the metal precursors with the olefin substrate (Eq. (1)) [16–18]. However, alkylidene intermediates were not observed in these systems, and cyclopropenes could not be used to activate them.



Within this context and with expertise in both cyclopropene and ruthenium chemistry present in the Grubbs group, the first member of a family of well-defined, metathesis-active ruthenium alkylidene complexes was born [1]. The successful reaction (Eq. (2)) was based on Lynda Johnson's work and carried out with a sample of her 3,3-diphenylcyclopropene. $(\text{PPh}_3)_2\text{Cl}_2\text{Ru}=\text{CH}-\text{CH}=\text{CPh}_2$ (**1a**) was synthesized starting from $\text{RuCl}_2(\text{PPh}_3)_3$, and we quickly found it to be a catalyst for the living ROMP of norbornene, as well as remarkably stable to water, acid, and many other functional groups. As anticipated, this complex is a five-coordinate, 16-electron, Ru(II) alkylidene species.



1.6.1.2

$(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CH}-\text{CH}=\text{CPh}_2$, A Well-Defined Ruthenium Alkylidene Catalyst for the Metathesis of Acyclic Olefins

After our initial publication about **1a** and its metathesis activity [1], progress slowed because **1a** could only polymerize highly-strained olefins. During this

period, I was influenced by the principles of early transition metal chemistry that I learned during my DuPont summer internship: in the Schrock systems, the more electron-withdrawing the ancillary ligands, the higher the catalytic activity [19–21]. Thus, we attempted to activate **1a** by replacing the chloride ligands with various electron-withdrawing anions, but with limited success. However, the results were encouraging enough that we worked under this premise for another six months [22].

I eventually became frustrated by these unsuccessful attempts and, running out of seemingly logical ideas, decided to ignore my early experience with the Schrock catalysts. Instead, we replaced the PPh_3 ligands of $(\text{PPh}_3)_2\text{Cl}_2\text{Ru}=\text{CH}-\text{CH}=\text{CPh}_2$ (**1a**) with PCy_3 (Cy = cyclohexyl), the most electron-donating phosphine in the stockroom. The resulting compound, $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CH}-\text{CH}=\text{CPh}_2$ (**2a**) was found to catalyze the metathesis of *cis*-2-pentene on September 28, 1992, almost one year after the initial experimental observation of $(\text{PPh}_3)_2\text{Cl}_2\text{Ru}=\text{CH}-\text{CH}=\text{CPh}_2$ [23]. As described in Chapter 1.11, the olefin metathesis mechanisms of these ruthenium complexes are quite different from early transition metal systems, and for this reason, history actually hindered our progress.

1.6.1.3

Initial Applications of Olefin Metathesis Chemistry Catalyzed by $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CH}-\text{CH}=\text{CPh}_2$

In retrospect, the applications of what are now called the 1st-generation Grubbs catalysts, $(\text{PR}'_3)_2\text{Cl}_2\text{Ru}=\text{CHR}$, would not have developed as quickly outside the Grubbs group during the years of 1992–1993. Bob maintains a diverse research group active in organic synthesis, polymer chemistry, organometallic chemistry, and materials science. It was within this collaborative and interdisciplinary environment that the significance of **1a** and **2a** was quickly realized. While I searched for a ruthenium complex to catalyze the metathesis of acyclic olefins, Gregory (Greg) Fu and Grubbs published a series of landmark papers on ring-closing metathesis (RCM) chemistry using the Schrock molybdenum catalysts [24–26]. I was fortunate to share a bench with Greg, and as soon as **2a** was found to catalyze the metathesis of acyclic olefins, Bob suggested that we move it into RCM chemistry. Greg had on hand a variety of RCM substrates and quickly found several cases where ruthenium was competitive with molybdenum. The two communications on the synthesis of **2a** and its use in RCM appeared together in print in July of 1992 [27, 28].

Synthetic polymer research using the new ruthenium-based catalysts also developed quickly. Marc Hillmyer, who was using tungsten catalyst to prepare telechelic polymers and functionalized ethylene/vinyl copolymers by ROMP, quickly converted to ruthenium. He also began experiments on the reaction-injection molding (RIM) of dicyclopentadiene (see Chapter 3.11). Other applications, such as fatty acid metathesis, acyclic diene metathesis polymerization (ADMET), and polyolefin depolymerization, soon followed [29].

Applications of **2a** in organic synthesis and polymer chemistry continued to expand within the Grubbs group. Parallel ene-yne-ene tandem cyclization to make fused bicyclic organic molecules was completed in 1994 [30]. The year 1995 saw the synthesis of eight-membered rings [31] and macrocyclization to cyclic peptides [32]. The ROMP of functionalized cyclobutenes [33] and polymerizations in biphasic media were also carried out successfully by 1995. We also were fortunate to see applications quickly developed by other research groups, largely because Bob was generous with sending out samples of **2a**. For example Hoveyda and coworkers used **2a** in an early kinetic resolution of pyrans [34]. In addition, the relatively straightforward synthesis and handling of **2a** encouraged researchers around the world to make it for their own use. Among other applications, Pandit used **2a** to construct the macrocyclic ring D of Manzamine A [35], Huwe and Blechert applied ruthenium-based RCM to construct aza-sugars [36], and Kinoshita and Mori used ruthenium catalysts for enyne cyclizations [37].

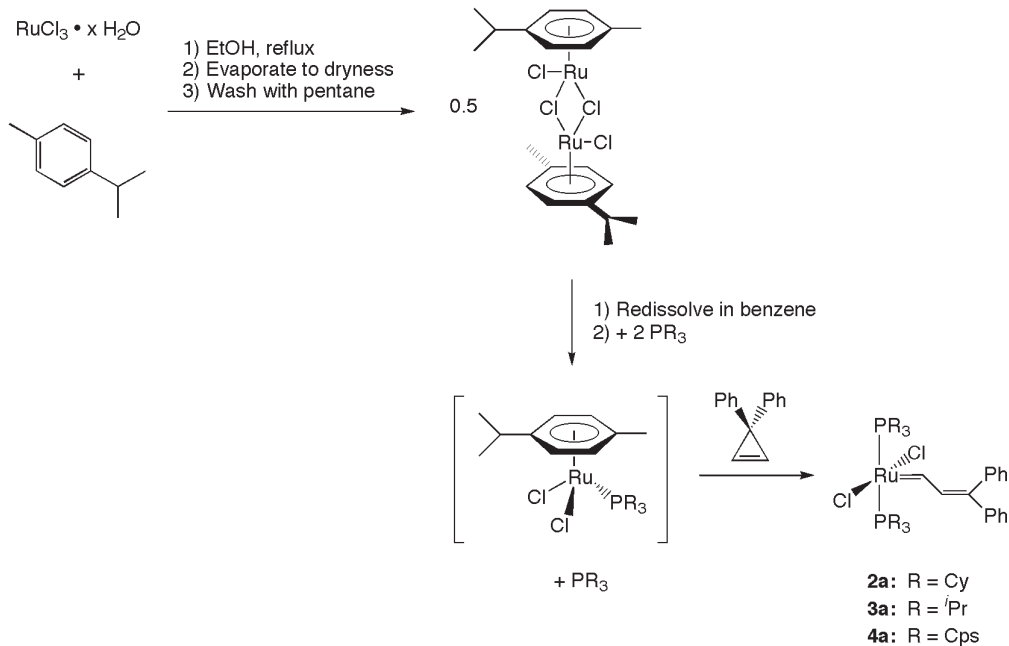
1.6.2

More Accessible Ruthenium Alkylidene Sources

With the $L_2X_2Ru=CHR$ structure identified and characterized as a functional group compatible yet metathesis-active target, a variety of catalyst syntheses were developed. The continuing goal is to identify $L_2X_2Ru=CHR$ -based structures that are easy to prepare and retain desirable qualities. For example, the greatly increased demand for **2a** that resulted from newly emerging applications of ruthenium-catalyzed olefin metathesis was met with the one-pot route in Scheme 1.6-1 [38].

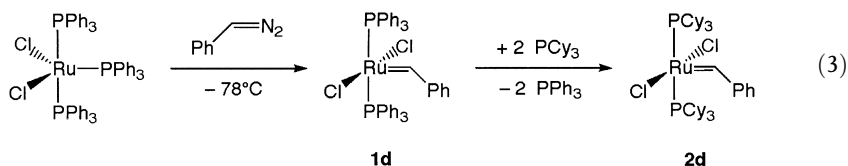
Two other routes that have been used to produce commercial-scale quantities of ruthenium catalyst include the use of diazo-transfer chemistry and the rearrangement of vinyl or propargyl halides. Although the synthesis in Scheme 1.6-1 can produce multi-grams quantities of **2a**, this amount does not meet commercial needs (including catalyst sales and large-scale polymer applications). In addition, despite the optimization of several 3,3-disubstituted cyclopropene syntheses, they remain quite time-consuming to make. Lastly, the vinylalkylidene group of **2a** is not an efficient initiator in all applications (see Chapter 1.10) and can be improved upon.

The first truly large-scale synthesis of a ruthenium alkylidene catalyst employed diazoalkanes as the alkylidene precursor [39]. Although alkyldiazomethanes are somewhat unstable, phenyldiazomethane can be handled safely on a large scale and prepared more efficiently than 3,3-diphenylcyclopropene. Phenyldiazomethane reacts rapidly with $Cl_2Ru(PPh_3)_3$ at $-78^\circ C$ to produce the ruthenium benzyldiene complex $(PPh_3)_2Cl_2Ru=CHPh$ (**1d**) (Eq. (3)) [40, 41]. Subsequent phosphine exchange with PCy_3 , in the same manner as with **1a**, produces $(PCy_3)_2Cl_2Ru=CHPh$ (**2d**) in high yield (>90%) and purity (>95%). Key to this synthesis is the insolubility of **2d** in acetone. The crude reaction mixture consists of the desired



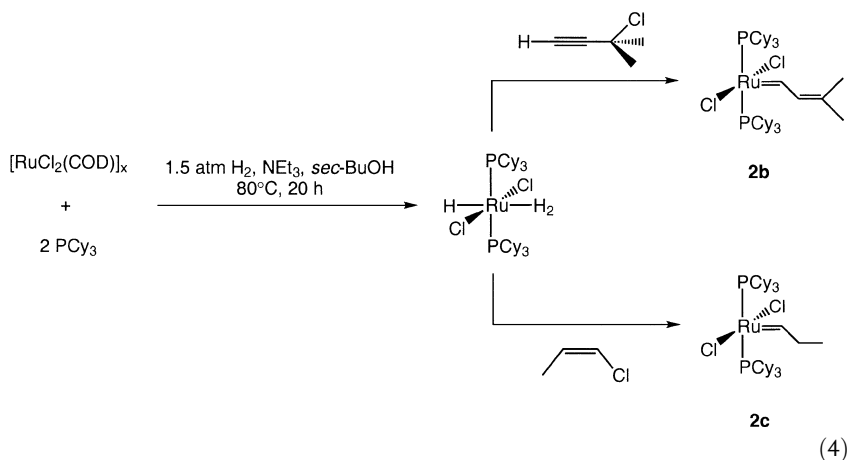
Scheme 1.6-1. A one-pot synthesis for **2a**, **3a**, and **4a**.
 (Cps = cyclopentyl, Cy = cyclohexyl, ⁱPr = isopropyl.)

product along with triphenylphosphine, diazo byproducts, and other impurities. Fortunately, all of these impurities are soluble in acetone whereas **2d** is not, so that simply washing the crude product with acetone produces sufficiently pure **2d** for most applications. Mike Giardello, in particular, played a major role in the scale-up of this process by developing methods to prepare and handle diazo precursors on a large scale and by streamlining the entire synthetic procedure. This methodology is used to produce kilogram quantities of catalyst **2d**. The relative ease of the synthesis, the high catalytic activity of **2d**, and its broad functional group tolerance have made **2d** the “workhorse” catalyst in olefin metathesis applications. Currently, **2d** is readily available commercially.



The rearrangement of vinyl or propargyl halides provides an additional route to ruthenium alkylidene complexes [42]. This procedure utilizes readily available alkynes as alkylidene precursors and introduces the PCy_3 ligands directly in the first step (Eq. (4)). This advance eliminated the use of potentially explosive diazo

compounds and shortened the catalyst synthesis by bypassing the phosphine exchange step and reducing the extensive washings required in earlier preparations. These improvements also resulted in a catalyst available at significantly reduced costs. This procedure is currently performed in one pot on the multi-kilogram scale to produce the dimethylvinylalkylidene catalyst **2b** in >90% yield. **2b** is used predominantly in commercial applications of ruthenium-catalyzed olefin metathesis technology for polymeric materials synthesis.



Other variations of oxidative addition/acetylene rearrangement to form ruthenium alkylidene complexes have been reported. Wolf, *et al.* published a one-pot syntheses of **2d** and $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHMe}$ (**2e**) by the direct reduction of $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ with $\text{Mg}/\text{ClCH}_2\text{CH}_2\text{Cl}$ in THF in the presence of excess PCy_3 and H_2 at 60–85 °C [43]. The $[(\text{PCy}_3)_2(\text{H}_2)\text{HClRu} + \text{HPCy}_3\text{Cl}]$ mixture formed *in situ* reacts with either phenylacetylene or ethyne in the presence of excess water to give **2d** and **2e**, respectively, in ~75% yield. However, the use of the relatively expensive PCy_3 in excess decreases the attractiveness of this route. Van der Schaaf and co-workers suggested a one-pot procedure for the synthesis of $(\text{P}^i\text{Pr}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ (**3d**) without the use of H_2 [44, 45], involving the *in situ* formation of a highly reactive ruthenium precursor from $[\text{RuCl}_2(\text{COD})]$ and two equivalents of P^iPr_3 in boiling isopropanol, followed by reaction with HCl , an alkyne, and styrene.

Two other methods for the synthesis of $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHR}$ have been reported. Olivan and Caulton carried out an unprecedented oxidative addition of both C–Cl bonds of CH_2Cl_2 to the $(\text{PCy}_3)_2(\text{H})_2(\text{H}_2)_2\text{Ru}$ metal center, which serves as a source of zerovalent $[(\text{PCy}_3)_2\text{Ru}]$. Notably, this route provides a convenient alternative synthesis of $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CH}_2$ (**2f**) [46]. In addition, Milstein and coworkers have employed sulfur ylides as alkylidene transfer agents. Direct reaction of $\text{Ph}_2\text{S}=\text{CHPh}$ with $(\text{PPh}_3)_2\text{Cl}_2\text{Ru}$ followed by *in situ* phosphine exchange with a slight excess of PCy_3 (2.15 equiv.) afforded **2d** in 96% yield [47]. For a variety of reasons, such as reaction yields, ease of scale-up, or cost of starting materials, none of these routes have been practiced commercially.

1.6.3

2nd-Generation Grubbs Catalysts

Although these $(PR'_3)_2Cl_2Ru=CHR$ catalysts were quite good at mediating olefin metathesis chemistry, Bob continued to insist that their activity and efficiency could be improved even further. He believed, for example, that the metathesis of tri- and tetra-substituted olefins should be possible with ruthenium(II) alkylidene complexes. He also wanted to bring their productivity in ROMP and RIM applications to the practical limit of 10^5 :1 monomer:catalyst ratio (established as the point at which RIM parts made using a ruthenium-based catalyst would be economically competitive). However, the majority of modifications to the phosphine ligands, the nature of the anionic ligands, and even the alkylidene moiety itself led to either incremental improvements or decreased catalyst activities [29, 48].

Metathesis-active $(PR'_3)_2Cl_2Ru=CHR$ complexes typically exhibit a distorted square pyramidal geometry with the alkylidene moiety in the apical site and a trans bis(phosphine) ligand arrangement at the base of the square pyramid (Figures 1.6-1 and 1.6-2, and Table 1.6-1). In contrast, five-coordinate ruthenium carbene complexes that contain strong π -acceptor ligands (e.g., CO), such as those made by Roper and coworkers (see Chapter 1.7), favor a trigonal bipyramidal geometry, and these complexes are not metathesis active.

Results from both the Grubbs group [22, 52–58] and others [59–71] suggest that even under the best circumstances, high catalytic activity often accompanies low catalyst stability, and vice versa. For example, complexes that contain chelating

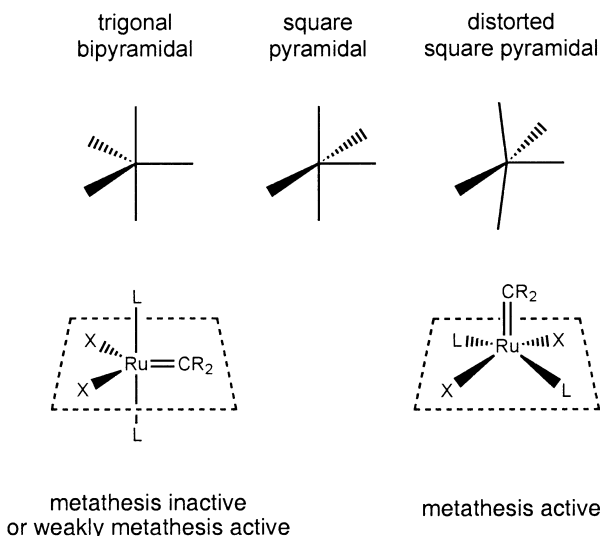


Fig. 1.6-1. The preferred geometry of metathesis-active ruthenium carbene complexes features a distorted square pyramidal geometry with the alkylidene moiety in the apical site and a trans bis(phosphine) ligand arrangement at the base of the square pyramid.

Tab. 1.6-1. Comparisons of bond lengths (Å) and angles (°) in seven representative $L_2X_2Ru=CHR$ complexes; all structures were determined by single crystal x-ray diffraction.

Complex	Ref	$Ru=C$	$Ru-Cl_{avg}$	$Ru-P$	$Ru-CN_2$	$Cl-Ru-Cl$	$L-Ru-P$	$Ru=C-R$
$(PCy_3)_2Cl_2Ru=CHPh$	49	1.838(2)	2.390(1)	2.416(1) _{avg}	–	168.21(2)	161.90(2)	136.7(2)
$(PCy_3)_2Cl_2Ru=CHCH_3$	49	1.816(2)	2.406(1)	2.410(1) _{avg}	–	173.65(2)	161.74(2)	132.7(2)
$(PCy_3)_2Cl_2Ru=CH(p-C_6H_4-Cl)$	41	1.839(3)	2.398(1)	2.416(1) _{avg}	–	167.6(1)	161.1(2)	136.0(2)
$(PCy_3)_2Cl_2Ru=CH-CHCPh_2$	27	1.852(21)	2.396(6)	2.418(7) _{avg}	–	173.4(2)	162.2(2)	129.2(16)
$(PPH_3)_2Cl_2Ru=CH-CHCPh_2$	1	1.887(7)	2.338(2)	2.387(2)	–	148.4(1)	166.5(1)	122.6(5)
$(H_2IMes)(PCy_3)Cl_2Ru=CHPh$	50	1.835(2)	2.395(1)	2.425(1)	2.085(2)	167.71(2)	163.73(6)	137.0(1)
$(H_2IMes)(PCy_3)Cl_2Ru=CH_2$	51	1.800(2)	2.386(1)	2.427(1)	2.065(2)	177.05(2)	165.81(5)	125.8(1) _{avg}

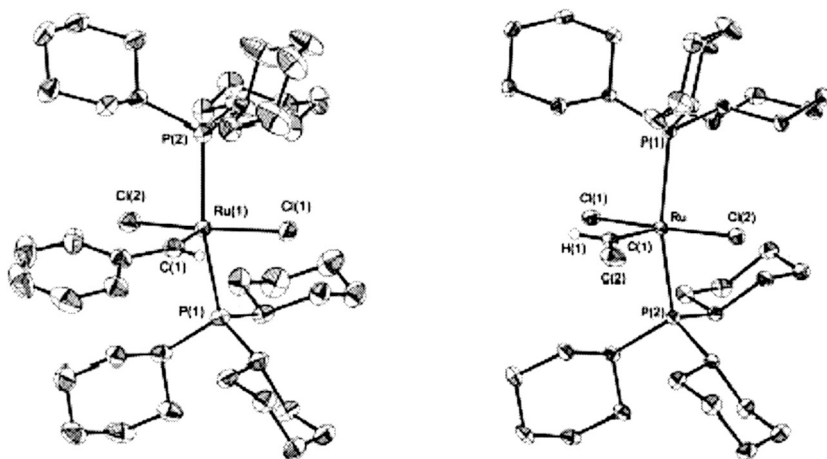


Fig. 1.6-2. Crystal structures of two representative $(PR'_3)_2X_2Ru=CHR$ complexes: $(PCy_3)_2Cl_2Ru=CHPh$ and $(PCy_3)_2Cl_2Ru=CHCH_3$.

or multidentate ligands, such as tris(pyrazolyl)borates [55], Schiff bases [54, 61], arenes [72–76], and bidentate phosphines [70, 77] (Figure 1.6-3, compounds **A–D**) generally show both low rates of initiation and low to moderate overall olefin metathesis activity. These effects are in some cases due to slow rates of ligand dissociation – a result of chelate stabilization – from the starting complexes, which leads to small concentrations of catalytically active species in solution. Another example, catalyst **H** with a chelating alkylidene alkoxy motif, often exhibits slow initiation rates for the same reason [64, 65, 71]. In contrast, the heterobimetallic [53] and pyridine-coordinated [78] complexes **E** and **F** (Figure 1.6-3) have very high activity, but this lasts for only a short time before the onset of catalyst decomposition. Complex **G** with a bridging alkylidene ligand [52] provides an additional challenge because of difficulties in forming a metallacyclobutane intermediate. Overall, these observations indicate that radical changes from the distorted square pyramidal trans-bis(phosphine) ligand arrangement of $(PR'_3)_2Cl_2Ru=CHR$ catalysts usually do not lead to improved olefin metathesis activity.

1.6.3.1

N-Heterocyclic Carbene (NHC) Ligands

Together with several mechanistic studies from the Grubbs group [22, 48, 79–83] and others [84–87], these results suggest that $(PCy_3)_2Cl_2Ru=CHPh$ forms a highly active mono(phosphine) intermediate during the catalytic cycle (see Chapter 1.10). This species is a good design motif and starting point for the development of more active catalyst derivatives (Figure 1.6-4). Unfortunately, the decomposition of $[(PCy_3)Cl_2Ru=CHPh]$ is known to be second-order and inversely proportional to phosphine concentration. Hence, attempts to achieve a greater concentration of the mono(phosphine) species from $(PCy_3)_2Cl_2Ru=CHPh$ with additives like CuCl and

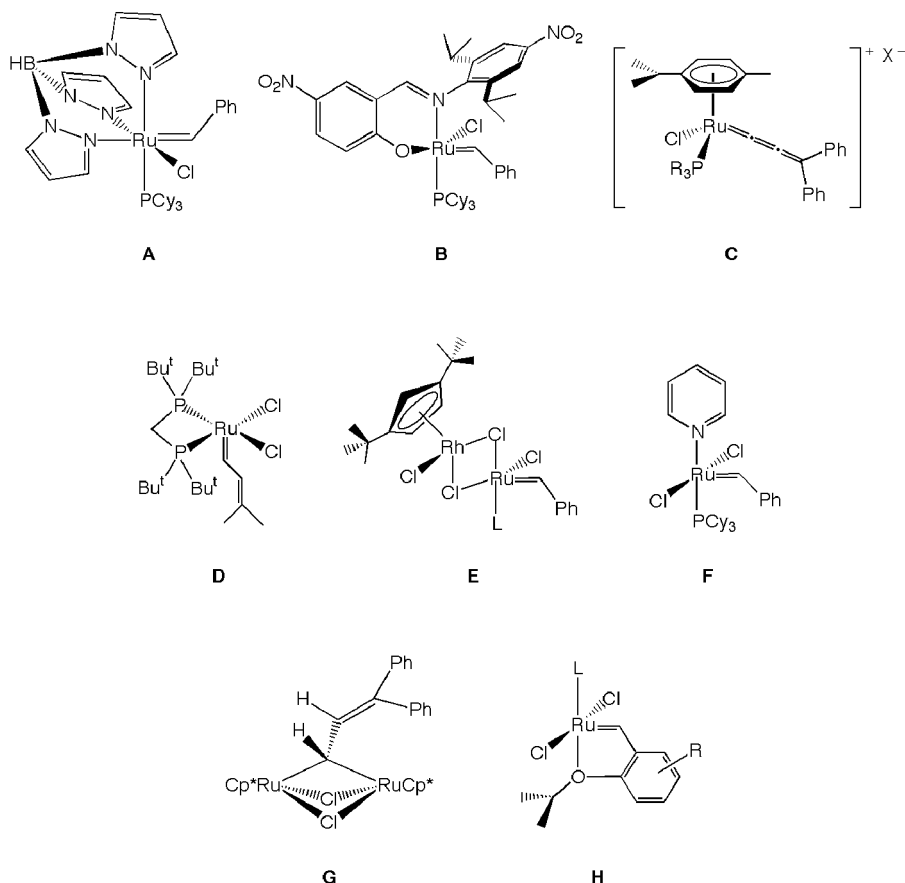


Fig. 1.6-3. Other well-defined, metathesis-active $L_2X_2Ru=CHR$ ruthenium alkylidene catalysts ($L = PR_3$ or NHC).

HCl result in enhanced catalytic activity but simultaneously promote catalyst decomposition [48, 88]. The important lesson is that any approach to increase the concentration of the mono(phosphine) intermediate is futile if it also accelerates decomposition. For this reason, an improved catalyst must contain ligands that can both stabilize the design motif and prevent decomposition of the parent ruthenium species at the same time.

Our interest in the potential of *N*-heterocyclic carbene (NHC) ligands as phosphine replacements [89–91] was prompted by the report of complex **5**, which was isolated from the reaction of **2d** with two equivalents of NHC (Figure 1.6-3, Eq. (5)) [92, 93]. This bis(NHC) derivative showed little improvement in activity compared to the bis(phosphine) complex **2d**. However, we believed that we could apply the design motif in Figure 1.6-4 to this system by making *monosubstituted* derivatives. Compared to phosphines, NHC ligands are stronger σ donors than phosphines and typically much less labile [89–91, 94]. Hence, in a mixed ligand complex such

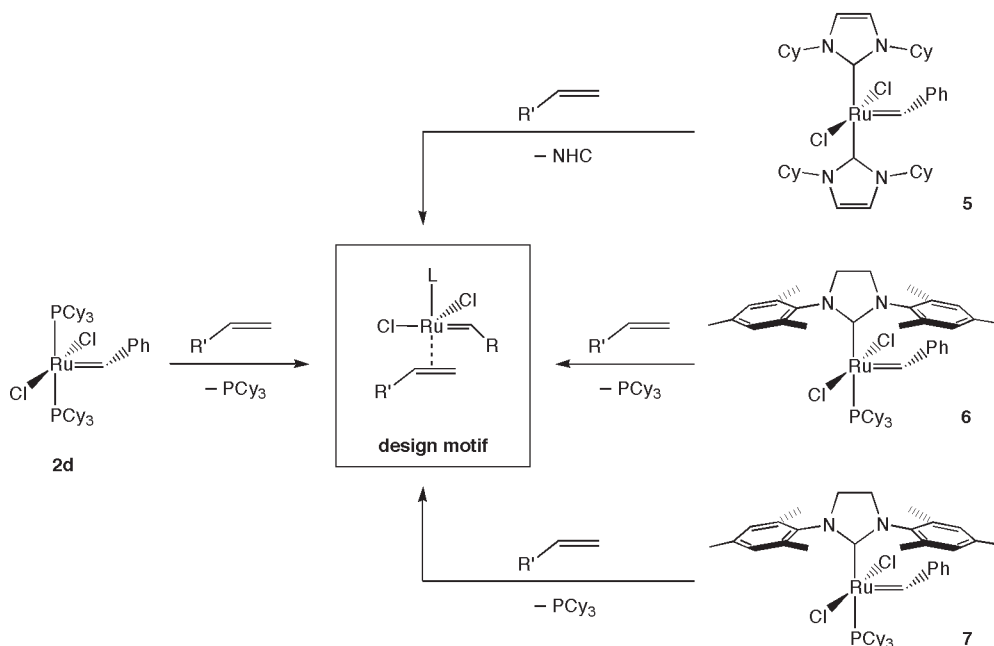
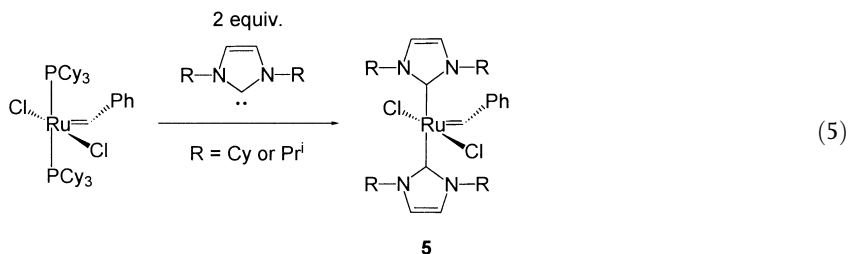


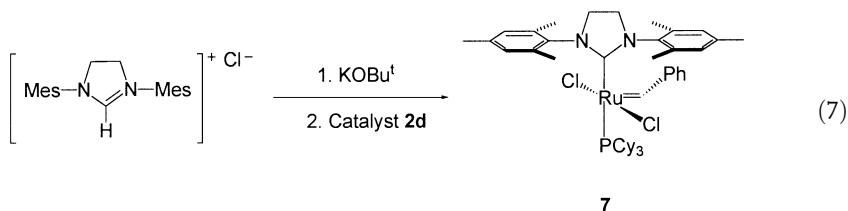
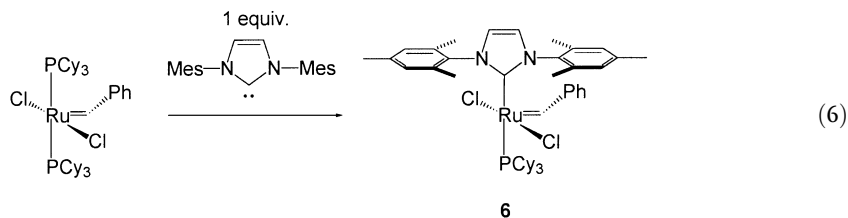
Fig. 1.6-4. Design motif for an ideal metathesis-active ruthenium alkylidene species, $(\text{olefin})(\text{L})\text{Cl}_2\text{Ru}=\text{CHR}$, and its generation from $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHR}$ and $(\text{NHC})(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHR}$ precursors.

as **6** or **7**, the NHC might enhance the dissociation of the trans phosphine from the metal center to yield the desired active species, which can then coordinate an olefin substrate. By virtue of its larger steric bulk and excellent electron-donating properties, the NHC ligand should stabilize both the 14-electron catalyst species and the 16-electron olefin complex more effectively, thus promoting olefin metathesis. This argument explains why the bis(NHC) complex **5** exhibited relatively low activity, since one of the NHC ligands would need to dissociate to produce a 14-electron intermediate.



This design rationale proved to be correct. Complexes **6** [95] and **7** [96] (Eqs. (6) and (7)) display fantastic catalytic performance and remarkable tolerance to air and an array of functional groups. Both catalysts are capable of effecting the metathesis

of tri- and tetra-substituted olefins [95, 96]. Additionally, both catalyze the RCM of diethyl diallylmalonate [96] and the ROMP of cyclooctadiene [97] at rates approximately 100–1000 times greater than those observed for **2d**. Complex **7**, in particular, has shown ROMP productivity at 10^5 :1 monomer:catalyst ratio, rivaling those of practical Ziegler–Natta systems. In a similar way, the groups of Herrmann [98–100] and Nolan [101] arrived at closely related complexes. Due to these amazing improvements, this class of catalyst has been called the “SuperGrubbs” or “2nd-generation Grubbs” catalysts [102]. Readers are invited to learn about the mechanism of these catalyst in Chapter 1.10 and their activity in the application chapters of this book.



1.6.4

Multi-Component Ruthenium-Based Olefin Metathesis Catalyst Systems and Homogeneous Catalyst Precursors

The development and application of several non-alkylidene ruthenium-based olefin metathesis systems occurred prior to and parallel with the development of well-defined catalysts. These systems can be divided into three classes: (1) homogeneous ruthenium precursors that form olefin or alkylidene complexes upon exposure to olefin substrates, (2) multi-component systems designed to generate more active ruthenium catalyst precursors *in situ*, and (3) homogeneous precursors that form metathesis-active ruthenium alkylidene species upon addition of a carbene source *in situ*. These systems are generally atom inefficient because not every metal center becomes active. Furthermore, they do not allow the fine control of selectivity that is the hallmark of well-defined ruthenium alkylidene catalysts. In the early days of ruthenium-based metathesis chemistry, these systems did offer an economic advantage over well-defined catalysts because they involve simple recipes than can be put together with commercially available compounds. However, the commercial availability of catalysts **2b**, **2d**, **6**, and **7** at increasingly lower costs has diminished this advantage.

A compilation of multi-component ruthenium-based systems and homogeneous ruthenium precursors is presented in Table 1.6-2. Entries 1 to 16 consist of various ruthenium salts, coordination compounds, and organometallic complexes, which generally catalyze the ROMP of the most highly-strained monomers (*i.e.*, norbornene and oxonorbornene derivatives) but not more challenging cases (*e.g.*, cyclooctene). Of these, $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ and $[\text{Ru}(\text{H}_2\text{O})_6][\text{tos}]_2$ have been used most widely. In particular, Kiessling and coworkers have synthesized a variety of carbohydrate-functionalized poly(oxonorbornenes) with the $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ system [103–105].

These olefin metathesis initiators are active without additional co-catalysts, but studies indicate that ruthenium–olefin complexes are generated when $[\text{Ru}(\text{H}_2\text{O})_6][\text{Tos}]_2$ is exposed to olefins in water (*vide supra*) [11, 16]. For example, the reaction of $[\text{Ru}(\text{H}_2\text{O})_6][\text{Tos}]_2$ and a carboximide-functionalized oxanorbornene produces the corresponding olefin complex (Figure 1.6-5a), which has been characterized by NMR spectroscopy [11]. In another case, the reaction of $[\text{Ru}(\text{H}_2\text{O})_6][\text{Tos}]_2$ with 3-pentenoic acid provides a bis(olefin) complex (Figure 1.6-5b), which is sufficiently stabilized so that it could be structurally characterized by x-ray diffraction [16]. The subsequent rearrangement of these olefin adducts to ruthenium alkylidene or ruthenacyclobutane complexes would provide the necessary initiator species for olefin metathesis. However, these rearrangements have not been observed to date.

Entries 17 to 20 in Table 1.6-2 include multi-component systems designed to generate a more active ruthenium initiator *in situ*. For example, the combination of $[\text{RuCl}_2(p\text{-cymene})]_2$, $[\text{NHC}(\text{H})][\text{Cl}]$, and Cs_2CO_3 (entry 19) generates monomeric $\text{RuCl}_2(p\text{-cymene})(\text{NHC})$ in solution, which when initiated for olefin metathesis, is a more active catalyst than $[\text{RuCl}_2(p\text{-cymene})]_2$ alone. These *p*-cymene complexes may initiate in the presence of olefin substrates upon loss of the *p*-cymene ligand by either thermal activation or irradiation (entries 17, 18, and 20).

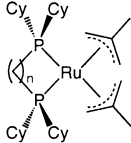
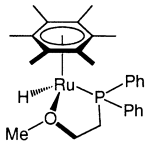
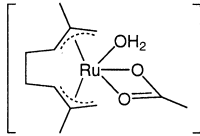
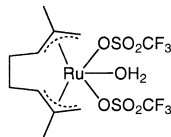
Entries 21 to 25 in Table 1.6-2 consist of ruthenium complexes that can be activated for olefin metathesis upon addition of catalytic amounts of a carbene source, such as a terminal alkyne, trimethylsilyldiazomethane, or ethyl diazoacetate. In these cases, the active ruthenium–carbene species is generated *in situ*. For example, a characteristic downfield ^1H NMR resonance (δ 17.92), typical of a ruthenium alkylidene α -proton, has been observed in the reaction of $(\text{PPh}_3)_3\text{RuCl}_2$ with ethyl diazoacetate and assigned to the formation of a $[\text{Ru}=\text{CH}(\text{CO}_2\text{Et})]$ moiety [12]. These catalyst systems are usually more active than those without discrete carbene-containing additives, and can mediate RCM reactions and the ROMP of cyclooctene.

1.6.5

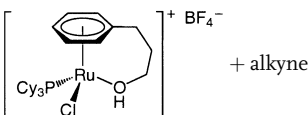
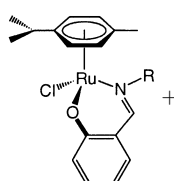
Solid-Supported Ruthenium-Based Olefin Metathesis Catalysts

Solid-supported homogeneous catalysts or heterogenized homogeneous catalysts, a popular research subject during the early 1970s [133–138], has seen a recent

Tab. 1.6-2. Ruthenium-based multi-component catalyst systems and homogeneous catalyst precursors for olefin metathesis.

Entry	Catalyst System	Catalytic Activity	References
1	$\text{RuCl}_3 \cdot \text{H}_2\text{O}$	ROMP of norbornene and oxonorbornene derivatives	8, 103–111
2	$[\text{Ru}(\text{H}_2\text{O})_6][\text{tos}]_2$	ROMP of norbornene and oxonorbornene derivatives ROMP of oxonorbornene derivatives and chain transfer with acyclic olefins ROMP of norbornene	7, 11, 106, 107, 112 13 113
3	$\text{Ru}(\eta^6\text{-benzene})(\text{H}_2\text{O})_3(\text{tos})_2$	ROMP of norbornene and oxonorbornene derivatives	106, 107
4	$\text{Ru}(\text{COD})\text{Cl}_3$	ROMP of oxonorbornene derivatives	8
5	$[\text{RuCl}_5(\text{H}_2\text{O})][\text{K}]_2$	ROMP of oxonorbornene derivatives	112, 114
6	ill-defined $[\text{Ru}(\text{TFA})]$ and $[\text{Ru}(\text{COD})]$	ROMP of oxonorbornene derivatives	114
7		ROMP of norbornene	115
8		ROMP of norbornene	116
9	 $^+ \text{BF}_4^-$	ROMP of norbornene	117
10		ROMP of norbornene	117
11	$\text{Ru}(\text{acac})$	CM of vinyl-substituted silanes	118
12	$[\text{RuCl}_2(\text{CO})_3]_2$	CM of vinyl-substituted silanes	118
13	$\text{Ru}_3(\text{CO})_{12}$	CM of vinyl-substituted silanes	118
14	$[\text{RuCl}_2(p\text{-cymene})]_2$	CM of vinyl-substituted silanes	118
15	$\text{RuCl}_2(p\text{-cymene})(\text{PR}_3)$	ROMP of norbornene RCM reactions	119 74, 120
16	$\text{RuCl}_2(p\text{-cymene})(\text{NHC})$	RCM of diethyl diallylmalonate	74

Tab. 1.6-2. (continued)

Entry	Catalyst System	Catalytic Activity	References
17	$[\text{RuCl}_2(p\text{-cymene})]_2 + \text{PCy}_3 + \text{neon light}$	RCM reactions	120
18	$\text{RuCl}_2(p\text{-cymene})(\text{PCy}_3) + \text{UV light}$	ROMP of norbornene	119
19	$[\text{RuCl}_2(p\text{-cymene})]_2 + [\text{NHC}(\text{H})][\text{Cl}] + \text{Cs}_2\text{CO}_3$	Enyne metathesis	121–124
20	$\text{RuCl}_2(p\text{-cymene})(\text{NHC}) + h\nu$	ROMP of cyclooctene	125
21		RCM reactions	126
22	$[\text{RuCl}_2(p\text{-cymene})]_2 + \text{alkyne}$	ROMP of norbornene	127–129
23	 trimethylsilyldiazomethane	RCM reactions	130
24	$[\text{Ru}(\text{H}_2\text{O})_6][\text{tos}]_2 + \text{ethyl diazoacetate}$	ROMP of cyclooctene and cyclopentene	12
25	$\text{RuCl}_2(p\text{-cymene})(\text{PR}_3) + \text{trimethylsilyldiazomethane}$	ROMP of norbornene and cyclooctene derivatives	131, 132

Abbreviations: tos = *p*-toluenesulfonate; TFA = trifluoroacetate; NHC = *N*-heterocyclic carbene; COD = 1,5-cyclooctadiene; ROMP = ring-opening metathesis polymerization; CM = cross metathesis; RCM = ring-closing metathesis.

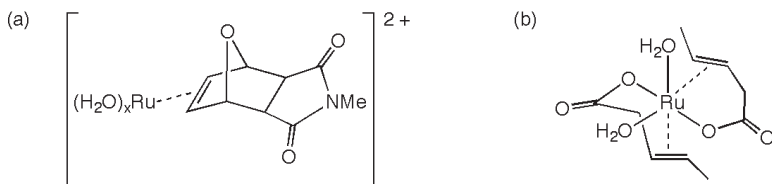


Fig. 1.6-5. Ruthenium–olefin complexes that result from the reactions of olefins with $[\text{Ru}(\text{H}_2\text{O})_6][\text{tos}]_2$ in water.

resurgence of interest during the last decade because it potentially offers the combined advantages of homogeneous catalysts (mild reaction conditions, selectivity, tunability, and the ability to access all sites) with those of heterogeneous catalysts (recyclability, amenable to high-throughput processes, easier product separation,

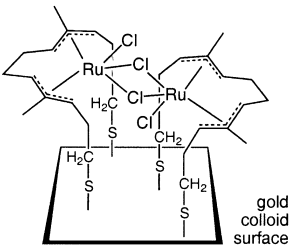
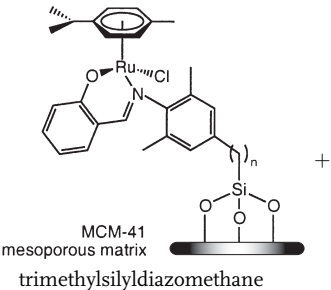
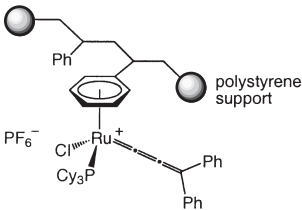
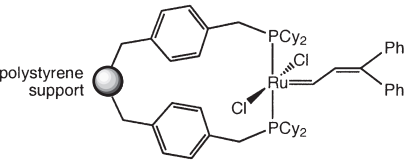
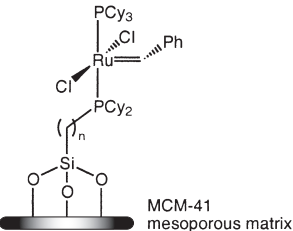
greater stability). In the case of the Grubbs ruthenium olefin metathesis catalysts, their simple ligand environment, functional group tolerance, and wide range of applications have offered a unique opportunity for chemists to support them on a variety of materials.

Table 1.6-3 compiles the major metathesis-active, ruthenium-based supported catalysts. Although compounds of the type discussed in section 1.6.4 (Table 1.6-3, entries 1 and 2) can be supported and shown to be metathesis active, our discussion will be limited to those $LL'X_2Ru=CHR$ cases where the modes of attachments are easily classified in the following three categories: (1) attachment through the anionic ligands X, (2) attachment through the ancillary ligand L or L', or (3) attachment through the alkylidene moiety. To date there is only one example of the first attachment strategy (Table 1.6-3, entry 8), and the initial results are quite promising.

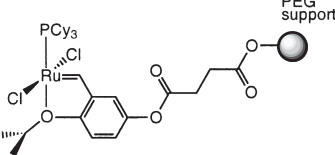
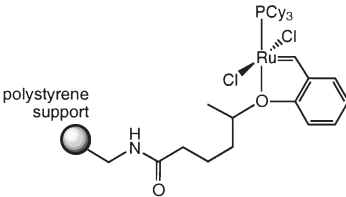
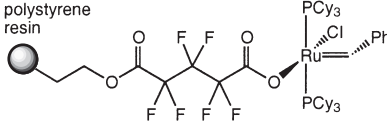
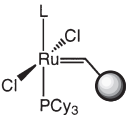
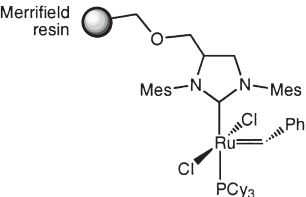
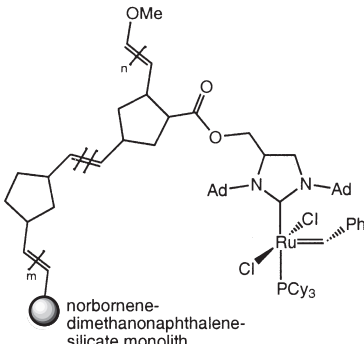
For the second strategy, attachment of the catalyst through both ancillary ligands, as that shown in entry 4, tends to reduce catalytic activity because such a configuration hinders the loss of one ancillary ligand that is necessary for catalyst activation. On the other hand, attachment through only one potentially labile ancillary ligand (Table 1.6-3, entry 5) creates the risk of catalyst leaching from the support: either the unattached phosphine or the attached phosphine can be dissociate from the metal center, with the latter leading to loss of the metal complex. From a strategic viewpoint, attachment of the catalyst through a non-labile ligand, such as the NHC moiety in a $(NHC)(PR'_3)_2X_2Ru=CHR$ derivative (Table 1.6-3, entries 10–11), affords the best chance of retaining the metal complex on the support; in this scenario, only the phosphine would be labilized during a catalytic cycle.

In the majority of cases (entries 6, 7, 12–13), the ruthenium complex is attached to the support through the alkylidene moiety. Unfortunately, with this connectivity the ruthenium complex is necessarily freed from the support after one catalytic turnover. This is impossible to avoid as dictated by the Chauvin mechanism for productive olefin metathesis. Claims of “boomerang” catalyst species that detach from the support, catalytically turn over, and then reattach to the support have not been supported by rigorous metal recovery analysis, *in situ* monitoring of the concentration of active species, and detailed kinetic studies. Similarly, claims of recyclability in these systems often have been made based solely on measurements of reaction yields at high conversions, which mean little due to the lapsing of too many half-lives. More rigorous evidence of recyclability could include both metal recovery analysis and reaction rate measurements at low conversions. It is likely that most of the catalytic activity observed in these cases is due to a small amount of $(NHC)_2X_2Ru=CHR$ catalyst species freed after the first turn-over cycle, which propagates very quickly. Because $(NHC)(PR'_3)_2X_2Ru=CHR$ complexes are known to be sluggish initiators, supported catalyst of this type are essentially slow-release reservoirs of catalyst. These properties can be potentially quite useful in slow-release or self-healing applications. However, they should not be confused with classic solid-supported homogeneous catalysts, which can be recovered and recycled without loss of the active species.

Tab. 1.6-3. Solid-supported ruthenium catalysts for olefin metathesis.

Entry	Catalyst	Catalytic Activity	Reference
1	 <p>gold colloid surface</p>	ROMP of norbornene	139
2	 <p>MCM-41 mesoporous matrix trimethylsilyldiazomethane</p>	ROMP of norbornene and cyclooctene, RCM reactions	140
3	 <p>polystyrene support</p>	RCM reactions	141
4	 <p>polystyrene support</p>	ROMP of cyclooctene, CM of cis-2-pentene	142
5	 <p>MCM-41 mesoporous matrix</p>	ROMP and RCM reactions	143

Tab. 1.6-3. (continued)

Entry	Catalyst	Catalytic Activity	Reference
6		RCM reactions	144
7		CM and RCM reactions	145
8		CM and RCM reactions	146
9	 <p>L = PR₃ or NHC</p> <p>poly(divinylbenzene) or vinylpolystyrene support</p>	CM and RCM reactions ROMP of norbornene derivatives, RCM reactions	147, 148 149–151
10		RCM and enyne metathesis reactions	152
11	 <p>norbornene- dimethanonaphthalene- silicate monolith</p>	ROMP of norbornene and cyclooctene, RCM reactions	153

Tab. 1.6-3. (continued)

<i>Entry</i>	<i>Catalyst</i>	<i>Catalytic Activity</i>	<i>Reference</i>
12	<p>PEDA-NH₂ resin</p>	CM and RCM reactions	154
13	<p>glass sol-gel support</p>	RCM and ROCM reactions	155

Abbreviations: Mes = mesityl; Ad = adamantyl; ROCM = ring-opening cross metathesis; PEG = poly(ethylene glycol).

1.6.6 Conclusions

The chronicle of well-defined, ruthenium-based olefin metathesis catalysts over the last decade has developed quickly and is full of excitement. It is a compelling example of how an ill-defined catalytic reaction, the RuCl_3 -mediated aqueous ROMP of 7-oxonorbornene, has been transformed into a set of well-defined tools with myriad applications in synthetic chemistry. The discovery and development of complex **1a** was made possible by the work of pioneers in olefin metathesis and metal carbene chemistry, including the groups of Binger, Roper, Schrock, Grubbs, and numerous others. Similarly, the development of 2nd-generation Grubbs catalysts would not have been conceivable without the fundamental contributions of Lappert, Wanzlick, Lemal, Arduengo, Herrmann, and others. Also key to the rapid development of these ruthenium catalysts once they were discovered was the desire of the Grubbs group to understand the mechanism of these systems, to improve catalytic activity and selectivity, to develop new catalyst preparations, and to demonstrate their utility in organic, polymer, and materials chemistry. Remarkably, the discovery of ruthenium alkylidene catalysts passed from the academic laboratory environment into the commercial arena and then the consumer-products market in less than a decade!

Ruthenium alkylidene complexes are the most functional group tolerant among all well-defined olefin metathesis catalysts to date. Together with their early transi-

tion metal cousins, ruthenium catalysts provide a range of synthetic tools. Each member of this diverse set has its own particular usefulness, which is important because olefin metathesis research has been driven largely by expanding technological applications.

Fundamentally, much remains to be discovered in the field of late transition metal-mediated olefin metathesis. Finding new and improved ways to prepare metal alkylidene complexes, modify ligand environments, and access other oxidation states of the ruthenium center by redox processes may further improve existing catalysts. In addition, other metal centers remain to be explored. Although ruthenium is one of least expensive precious metals, its cost is not insignificant. A challenge will be to find a well-defined, metathesis-active alkylidene complex of a more common metal, such as iron. We are confident that with the right design and ligand environment, it is only a matter of time before such species appear. We look forward to these exciting future developments!

References

- 1 NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975.
- 2 Feast also commented about the challenge of making these early Schrock catalysts: “*There is a penalty to be paid for the intending participant in this activity in as much as the synthesis and use of these newer catalysts places experimental skill at a premium.*” See: FEAST, W. J. In *Comprehensive Polymer Science*; ALLEN, G.; BEVINGTON, J. C., Eds.; Pergamon Press: New York, 1989; Vol. 4, Chapter 7, pp 135–142.
- 3 JOHNSON, L. K.; VIRGIL, S. C.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 5384–5385.
- 4 JOHNSON, L. K.; FREY, M.; ULIBARRI, T. A.; VIRGIL, S. C. *J. Am. Chem. Soc.* **1993**, *115*, 8167–8177.
- 5 JOHNSON, L. K., Ph.D. Thesis, California Institute of Technology, 1992.
- 6 JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8130–8145.
- 7 NOVAK, B. M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542–7543.
- 8 NOVAK, B. M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960–961.
- 9 IVIN, K. J. *Olefin Metathesis*; Academic Press: London, 1983.
- 10 NOVAK, B. M., Ph.D. Thesis, California Institute of Technology, 1989.
- 11 HILLMYER, M. A.; LEPETIT, C.; MCGRATH, D. V.; NOVAK, B. M.; GRUBBS, R. H. *Macromolecules* **1992**, *25*, 3345–3350.
- 12 FRANCE, M. B.; PACIELLO, R. A.; GRUBBS, R. H. *Macromolecules* **1993**, *26*, 4739–4741.
- 13 FRANCE, M. B.; GRUBBS, R. H.; MCGRATH, D. V.; PACIELLO, R. A. *Macromolecules* **1993**, *26*, 4742–4747.
- 14 BERNHARD, P.; LEHMANN, H.; LUDI, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1216–1217.
- 15 BERNHARD, P.; BUERGI, H. B.; HAUSER, J.; LEHMANN, H.; LUDI, A. *Inorg. Chem.* **1982**, *21*, 3936–3941.
- 16 MCGRATH, D. V.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 3611–3613.
- 17 MCGRATH, D. V., Ph.D. Thesis, California Institute of Technology, 1992.
- 18 MCGRATH, D. V.; GRUBBS, R. H. *Organometallics* **1994**, *13*, 224–235.
- 19 FELDMAN, J.; SCHROCK, R. R. *Prog. Inorg. Chem.* **1991**, *39*, 1–74.
- 20 SCHROCK, R. R. *Acc. Chem. Res.* **1986**, *19*, 342–348.
- 21 SCHROCK, R. R. *Acc. Chem. Res.* **1990**, *23*, 158–165.
- 22 WU, Z.; NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.

- 23 The first observation of $(\text{PPh}_3)_2\text{Cl}_2\text{Ru}=\text{CH}-\text{CH}=\text{CPh}_2$ was made on October 8, 1991.
- 24 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427.
- 25 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.
- 26 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800–3801.
- 27 NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.
- 28 FU, G. C.; NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
- 29 NGUYEN, S. T., Ph.D. Thesis, California Institute of Technology, 1995.
- 30 KIM, S. H.; BOWDEN, N. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801–10802.
- 31 MILLER, S. J.; KIM, S.-H.; CHEN, Z.-R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
- 32 MILLER, S. J.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855–5856.
- 33 MAUGHON, B. R.; GRUBBS, R. H. *Polym. Preprints* **1995**, *37*(1), 471–472.
- 34 MORKEN, J. P.; DIDIUK, M. T.; VISSER, M. S.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123–3124.
- 35 BORER, B. C.; DEERENBERG, S.; BIERAUGEL, H.; PANDIT, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191–3194.
- 36 HUWE, C. M.; BLECHERT, S. *Tetrahedron Lett.* **1995**, *36*, 1621–1624.
- 37 KINOSHITA, A.; MORI, M. *Synlett* **1994**, 1020–1022.
- 38 NGUYEN, S. T.; GRUBBS, R. H., California Institute of Technology, unpublished results.
- 39 For early examples of the reactions of diazo compounds with ruthenium precursors, see: FRANCE, M. B., Ph.D. Thesis, California Institute of Technology, 1995.
- 40 SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041.
- 41 SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- 42 WILHELM, T. E.; BELDERRAIN, T. R.; BROWN, S. N.; GRUBBS, R. H. *Organometallics* **1997**, *16*, 3867–3869.
- 43 WOLF, J.; STÜER, W.; GRÜNWALD, C.; WERNER, H.; SCHWAB, P.; SCHULZ, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1124–1126.
- 44 VAN DER SCHAAF, P. A.; KOLLY, R.; HAFNER, A. *Chem. Commun.* **2001**, 940.
- 45 VAN DER SCHAAF, P. A.; KOLLY, R.; HAFNER, A. *Chem. Commun.* **2000**, 1045–1046.
- 46 OLIVAN, M.; CAULTON, K. G. *Chem. Commun.* **1997**, 1733–1734.
- 47 GANDELMAN, M.; RYBTCHINSKI, B.; ASHKENAZI, N.; GAUVIN, R. M.; MILSTEIN, D. *J. Am. Chem. Soc.* **2001**, *123*, 5372–5373.
- 48 DIAS, E. L.; NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.
- 49 TRNKA, T. M., Ph.D. Thesis, California Institute of Technology, 2003.
- 50 LOVE, J. A.; SANFORD, M. S.; DAY, M. W.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2003**, *125*, in press.
- 51 TRNKA, T. M.; DAY, M. W.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3441–3444.
- 52 GAGNÉ, M. R.; GRUBBS, R. H.; FELDMAN, J.; ZILLER, J. W. *Organometallics* **1992**, *11*, 3933–3935.
- 53 DIAS, E. L.; GRUBBS, R. H. *Organometallics* **1998**, *17*, 2758–2767.
- 54 CHANG, S.; JONES, L.; WANG, C.; HENLING, L. M.; GRUBBS, R. H. *Organometallics* **1988**, *17*, 3460–3465.
- 55 SANFORD, M. S.; HENLING, L. M.; GRUBBS, R. H. *Organometallics* **1988**, *17*, 5384–5389.
- 56 LYNN, D. M.; MOHR, B.; GRUBBS, R. H.; HENLING, L. M.; DAY, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601–6609.
- 57 ULMAN, M.; BELDERRAIN, T. R.; GRUBBS, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689–4693.
- 58 SEIDERS, T. J.; WARD, D. W.; GRUBBS, R. H. *Org. Lett.* **2001**, *3*, 3225–3228.
- 59 DENK, K.; FRIDGEN, J.; HERRMANN, W. A. *Adv. Synth. Catal.* **2002**, *344*, 666–670.
- 60 OPSTAL, T.; COUCHEZ, K.; VERPOORT, F. *Adv. Synth. Catal.* **2003**, *345*, 393–401.
- 61 DE CLERCQ, B.; VERPOORT, F. *Adv. Synth. Catal.* **2002**, *344*, 639–648.

- 62 BUCHOWICZ, W.; INGOLD, F.; MOL, J. C.; LUTZ, M.; SPEK, A. L. *Chem. Eur. J.* **2001**, 7, 2842–2847.
- 63 COALTER, J. N., III; CAUTION, K. G. *New J. Chem.* **2001**, 25, 679–684.
- 64 GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2001**, 123, 3186.
- 65 GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, 122, 8168–8179.
- 66 KATAYAMA, H.; URUSHIMA, H.; NISHIOKA, T.; WADA, C.; NAGAO, M.; OZAWA, F. *Angew. Chem. Int. Ed.* **2000**, 39, 4513–4515.
- 67 LEUNG, W.-H.; LAU, K.-K.; ZHANG, Q.-F.; WONG, W.-T.; TANG, B. *Organometallics* **2000**, 19, 2084–2089.
- 68 SAUD, M.; ROMEROSA, A.; PERUZZINI, M. *Organometallics* **2000**, 19, 4005–4007.
- 69 VAN DER SCHAAF, P. A.; KOLLY, R.; KIRNER, H.-J.; RIME, F.; MÜHLEBACH, A.; HAFNER, A. *J. Organomet. Chem.* **2000**, 606, 65–74.
- 70 HANSEN, S. M.; VOLLAND, M. A. O.; ROMINGER, F.; EISENTRAGER, F.; HOFMANN, P. *Angew. Chem. Int. Ed.* **1999**, 38, 1273–1276.
- 71 KINGSBURY, J. S.; HARRITY, J. P. A.; BONITATEBUS, P. J., JR.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, 121, 791–799.
- 72 PICQUET, M.; BRUNEAU, C.; DIXNEUF, P. H. *Chem. Commun.* **1998**, 2249–2250.
- 73 FÜRSTNER, A.; PICQUET, M.; BRUNEAU, C.; DIXNEUF, P. H. *Chem. Commun.* **1998**, 1315–1316.
- 74 JAFARPOUR, L.; HUANG, J.; STEVENS, E. D.; NOLAN, S. P. *Organometallics* **1999**, 18, 3760–3763.
- 75 PICQUET, M.; TOUCHARD, D.; BRUNEAU, C.; DIXNEUF, P. H. *New J. Chem.* **1999**, 23, 141–143.
- 76 FÜRSTNER, A.; LIEBL, M.; LEHMANN, C. W.; PICQUET, M.; KUNZ, R.; BRUNEAU, C.; TOUCHARD, D.; DIXNEUF, P. H. *Chem. Eur. J.* **2000**, 6, 1847–1857.
- 77 HANSEN, S. M.; ROMINGER, F.; METZ, M.; HOFMANN, P. *Chem. Eur. J.* **1999**, 5, 557–566.
- 78 DIAS, E. L., Ph.D. Thesis, California Institute of Technology, 1998.
- 79 MAUGHON, B. R.; GRUBBS, R. H. *Macromolecules* **1997**, 30, 3459–3469.
- 80 CUCULLU, M. E.; LI, C.; NOLAN, S. P.; NGUYEN, S. T.; GRUBBS, R. H. *Organometallics* **1998**, 17, 5565–5568.
- 81 ULMAN, M.; GRUBBS, R. H. *Organometallics* **1998**, 17, 2484–2489.
- 82 ULMAN, M.; BELDERRAIN, T. R.; GRUBBS, R. H. *Tetrahedron Lett.* **2000**, 41, 4689–4693.
- 83 ULMAN, M.; GRUBBS, R. H. *J. Org. Chem.* **1999**, 64, 7202–7207.
- 84 TALLARICO, J. A.; BONITATEBUS, P. J.; SNAPPER, M. L. *J. Am. Chem. Soc.* **1997**, 119, 7157–7158.
- 85 HINDERLING, C.; ADLHART, C.; CHEN, P. *Angew. Chem. Int. Ed.* **1998**, 37, 2685–2689.
- 86 AAGAARD, O. M.; MEIER, R. J.; BUDA, F. *J. Am. Chem. Soc.* **1998**, 120, 7174–7182.
- 87 ADLHART, C.; HINDERLING, C.; BAUMANN, H.; CHEN, P. *J. Am. Chem. Soc.* **2000**, 122, 8204–8214.
- 88 TRNKA, T. M.; R. H. GRUBBS, *Acc. Chem. Res.* **2001**, 34, 18–29.
- 89 BOURISSOU, D.; GUERRET, O.; GABBAÏ, F. P.; BERTRAND, G. *Chem. Rev.* **2000**, 100, 39–91.
- 90 ARDUENGO, A. J. *Acc. Chem. Res.* **1999**, 32, 913–921.
- 91 HERRMANN, W. A.; KÖCHER, C. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2163–2187.
- 92 WESKAMP, T.; SCHATTENMANN, W. C.; SPIEGLER, M.; HERRMANN, W. A. *Angew. Chem. Int. Ed.* **1998**, 37, 2490–2493.
- 93 WESKAMP, T.; SCHATTENMANN, W. C.; SPIEGLER, M.; HERRMANN, W. A. *Angew. Chem. Int. Ed.* **1998**, 38, 262.
- 94 HUANG, J.; SCHANZ, H.-J.; STEVENS, E. D.; NOLAN, S. P. *Organometallics* **1999**, 18, 5375–5380.
- 95 SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. *Tetrahedron Lett.* **1999**, 40, 2247–2250.
- 96 SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 953–956.
- 97 BIELAWSKI, C. W.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2000**, 39, 2903–2906.

- 98 WESKAMP, T.; KOHL, F. J.; HERRMANN, W. A. *J. Organomet. Chem.* **1999**, 582, 362–365.
- 99 WESKAMP, T.; KOHL, F. J.; HIERINGER, W.; GLEICH, D.; HERRMANN, W. A. *Angew. Chem. Int. Ed.* **1999**, 38, 2416–2419.
- 100 ACKERMANN, L.; FÜRSTNER, A.; WESKAMP, T.; KOHL, F. J.; HERRMANN, W. A. *Tetrahedron Lett.* **1999**, 40, 4787–4790.
- 101 HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSEN, J. L. *J. Am. Chem. Soc.* **1999**, 121, 2674–2678.
- 102 STINSON, S. *Chem. Eng. News* **2000**, 78(35), 6–7.
- 103 MORTELL, K. H.; GINGRAS, M.; KIESSLING, L. L. *J. Am. Chem. Soc.* **1994**, 116, 12053–12054.
- 104 MORTELL, K. H.; WEATHERMAN, R. V.; KIESSLING, L. L. *J. Am. Chem. Soc.* **1996**, 118, 2297–2298.
- 105 SCHUSTER, M. C.; MORTELL, K. H.; HEGEMAN, A. D.; KIESSLING, L. L. *J. Mol. Catal. A: Chem.* **1997**, 116, 209–216.
- 106 MICHELOTTI, F. W.; KEAVENEY, W. P. *J. Polymer Sci., Pt. A* **1965**, 3, 895–905.
- 107 RINEHART, R. E.; SMITH, H. P. *J. Polymer Sci., Pt. B* **1965**, 3, 1049–1052.
- 108 MÜHLEBACH, A.; BERNHARD, P.; BÜHLER, N.; KARLEN, T.; LUDI, A. *J. Mol. Catal.* **1994**, 90, 143–156.
- 109 LU, S. Y.; QUAYLE, P.; HEATLEY, F.; BOOTH, C.; YEATES, S. G.; PADGET, J. C. *Macromolecules* **1992**, 25, 2692–2697.
- 110 FEAST, W. J.; HARRISON, D. B. *J. Mol. Catal.* **1991**, 65, 63–72.
- 111 THOI, H. H.; IVIN, K. J.; ROONEY, J. J. *J. Mol. Catal.* **1982**, 15, 245–270.
- 112 ZENKL, E.; STELZER, F. *J. Mol. Catal.* **1992**, 76, 1–14.
- 113 HAMILTON, J. G.; ROONEY, J. J.; DESIMONE, J. M.; MISTELE, C. *Macromolecules* **1998**, 31, 4387–4389.
- 114 MCGRATH, D. V.; NOVAK, B. M.; GRUBBS, R. H. In *Olefin Metathesis and Polymerization Catalysts*; IMAMOGLU, Y. Ed.; Kluwer Academic Publishers: Dordrecht, 1990; pp 525–536.
- 115 SIX, C.; BECK, K.; WEGNER, A.; LEITNER, W. *Organometallics* **2000**, 19, 4639–4642.
- 116 LINDNER, E.; PAUTZ, S.; FAWZI, R.; STEIMANN, M. *Organometallics* **1998**, 17, 3006–3014.
- 117 WACHE, S. *J. Organomet. Chem.* **1995**, 494, 235–240.
- 118 MARCINIEC, B.; FOLTYNOWICZ, Z.; PIETRASZUK, C.; GULINSKI, J.; MACIEJEWSKI, H. *J. of Mol. Catal.* **1994**, 90, 213–224.
- 119 HAFNER, A.; MÜHLEBACH, A.; VAN DER SCHAAF, P. A. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2121–2124.
- 120 FÜRSTNER, A.; ACKERMANN, L. *Chem. Commun.* **1999**, 95–96.
- 121 SEMERIL, D.; CLERAN, M.; PEREZ, A. J.; BRUNEAU, C.; DIXNEUF, P. H. *J. Mol. Catal. A: Chem.* **2002**, 190, 9–25.
- 122 SEMERIL, D.; BRUNEAU, C.; DIXNEUF, P. H. *Helv. Chim. Acta* **2001**, 84, 3335–3341.
- 123 SEMERIL, D.; CLERAN, M.; BRUNEAU, C.; DIXNEUF, P. H. *Adv. Synth. Cat.* **2001**, 343, 184–187.
- 124 ACKERMANN, L.; BRUNEAU, C.; DIXNEUF, P. H. *Synlett* **2001**, 397–399.
- 125 DELAUDE, L.; DEMONCEAU, A.; NOELS, A. F. *Chem. Commun.* **2001**, 986–987.
- 126 MIYAKI, Y.; ONISHI, T.; OGOSHI, S.; KUROSAWA, H. *J. Organomet. Chem.* **2000**, 616, 135–139.
- 127 KATAYAMA, H.; OZAWA, F. *Organometallics* **1998**, 17, 5190–5196.
- 128 KATAYAMA, H.; YOSHIDA, T.; OZAWA, F. *J. Organomet. Chem.* **1998**, 562, 203–206.
- 129 KATAYAMA, H.; OZAWA, F. *Chem. Lett.* **1998**, 67–68.
- 130 DE CLERCQ, B.; VERPOORT, F. *Tetrahedron Lett.* **2001**, 42, 8959–8963.
- 131 JAN, D.; DELAUDE, L.; SIMAL, F.; DEMONCEAU, A.; NOELS, A. F. *J. Organomet. Chem.* **2000**, 606, 55–64.
- 132 DEMONCEAU, A.; STUMPF, A. W.; SAIVE, E.; NOELS, A. F. *Macromolecules* **1997**, 30, 3127–3136.
- 133 GRUBBS, R. H.; KROLL, L. C. *J. Am. Chem. Soc.* **1971**, 93, 3062–3063.
- 134 GRUBBS, R. H. *Chemtech* **1977**, 7, 512–518.
- 135 GRUBBS, R. H. *Strem Chemiker* **1976**, 4, 3–7.
- 136 CORNILS, B.; HERRMANN, W. A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; CORNILS, B.

- AND HERRMANN, W. A. Eds.; VCH: Weinheim, 1996; Vol. 2; pp 575–601.
- 137 MICHALSKA, Z. M.; WEBSTER, D. E. *Platinum Met. Rev.* **1974**, 18, 65–73.
 - 138 PITTMAN, C. U., JR.; EVANS, G. O. *Chemtech* **1973**, 560–566.
 - 139 BARTZ, M.; KUTHER, J.; SESHADRI, R.; TREMEL, W. *Angew. Chem. Int. Ed.* **1998**, 37, 2466–2468.
 - 140 DE CLERCQ, B.; LEFEBVRE, F.; VERPOORT, F. *New J. Chem.* **2002**, 26, 1201–1208.
 - 141 AKIYAMA, R.; KOBAYASHI, S. *Angew. Chem. Int. Ed.* **2002**, 41, 2602–2604.
 - 142 NGUYEN, S. T.; GRUBBS, R. H. *J. Organomet. Chem.* **1995**, 497, 195–200.
 - 143 MELIS, K.; DE VOS, D.; JACOBS, P.; VERPOORT, F. *J. Mol. Catal. A: Chem.* **2001**, 169, 47–56.
 - 144 YAO, Q. *Angew. Chem. Int. Ed.* **2000**, 39, 3896–3898.
 - 145 DOWDEN, J.; SAVOVIC, J. *Chem. Commun.* **2001**, 37–38.
 - 146 NIECZYPOR, P.; BUCHOWICZ, W.; MEESTER, W. J. N.; RUTJES, F. P. J. T.; MOL, J. C. *Tetrahedron Lett.* **2001**, 42, 7103–7105.
 - 147 JAFARPOUR, L.; NOLAN, S. P. *Org. Lett.* **2000**, 2, 4075–4078.
 - 148 JAFARPOUR, L.; HECK, M.-P.; BAYLON, C.; LEE, H. M.; MIOSKOWSKI, C.; NOLAN, S. P. *Organometallics* **2002**, 21, 671–679.
 - 149 AHMED, M.; ARNAULD, T.; BARRETT, A. G. M.; BRADDOCK, D. C.; PROCOPIOU, P. A. *Synlett* **2000**, 1007–1009.
 - 150 AHMED, M.; BARRETT, A. G. M.; BRADDOCK, D. C.; CRAMP, S. M.; PROCOPIOU, P. A. *Tetrahedron Lett.* **1999**, 40, 8657–8662.
 - 151 BARRETT, A. G. M.; CRAMP, S. M.; ROBERTS, R. S. *Org. Lett.* **1999**, 1, 1083–1086.
 - 152 SCHURER, S. C.; GESSLER, S.; BUSCHMANN, N.; BLECHERT, S. *Angew. Chem. Int. Ed.* **2000**, 39, 3898–3901.
 - 153 MAYR, M.; MAYR, B.; BUCHMEISER, M. R. *Angew. Chem. Int. Ed.* **2001**, 40, 3839–3842.
 - 154 CONNON, S. J.; BLECHERT, S. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1873–1876.
 - 155 KINGSBURY, J. S.; GARBER, S. B.; GIFTOS, J. M.; GRAY, B. L.; OKAMOTO, M. M.; FARRER, R. A.; FOURKAS, J. T.; HOVEYDA, A. H. *Angew. Chem. Int. Ed.* **2001**, 40, 4251–4256.

1.7

Synthesis of Ruthenium Carbene Complexes

Warren R. Roper

1.7.1

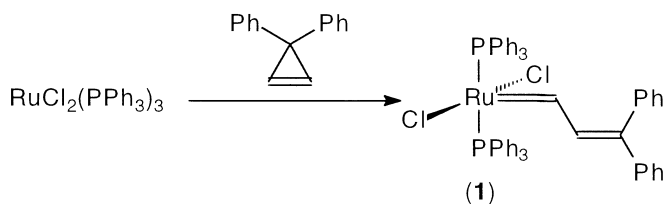
Introduction

The discovery, reported by Grubbs and coworkers in 1992 [1], that ruthenium(II) carbene complexes of the type $\text{RuX}_2(=\text{CHR})\text{L}_2$ (X = anionic ligand, L = tertiary phosphine) are active catalysts (or pre-catalysts) for alkene metathesis was a major development in organometallic catalysis. The defining characteristics of the first catalyst, $\text{RuCl}_2(=\text{CHCH}=\text{CPh}_2)(\text{PPh}_3)_2$ (**1**) (see Scheme 1.7-1), and indeed most of the refined and improved catalysts that were later discovered, were all similar. From a structural inorganic point of view, the key features of the catalyst were the presence of (1) an alkylidene ligand (or carbene ligand without heteroatom substituents), (2) two mutually *trans* triphenylphosphine or related ligands, (3) two chloride or other anionic ligands, and (4) coordinative unsaturation, with the five-coordinate, 16-electron complex displaying approximately tetragonal pyramidal geometry and the vacant site *trans* to the alkylidene ligand. In this brief article I will trace, in a historical sense, some of the early discoveries in ruthenium(II) carbene complex chemistry that provide examples of the features listed above and in general give the more “inorganic” background for understanding the emergence of the Grubbs catalysts. Occasionally, reference will be made also to the related osmium(II) carbene complexes.

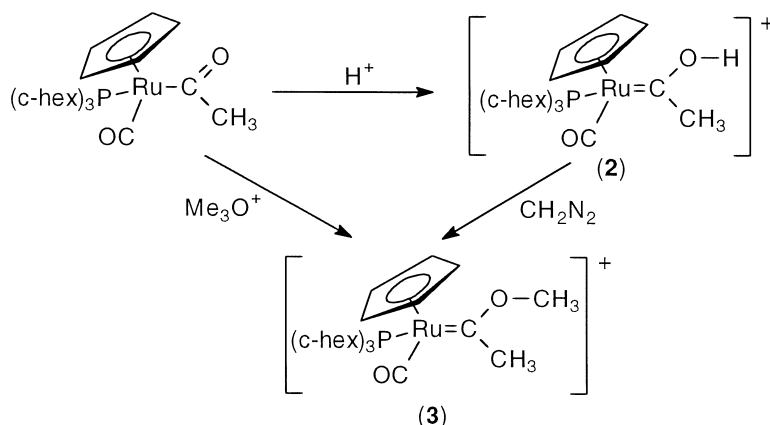
1.7.2

The First Ruthenium Carbene Complexes

Seven years would elapse after E. O. Fischer’s groundbreaking report of Group VI metal carbene complexes [2] before the first ruthenium(II) carbene complexes were described by Green and coworkers [3] in 1971. The synthetic approach was essentially the same as Fischer’s: protonation of a metal acyl derivative to give the hydroxy carbene complex **2** or alkylation to give **3** (Scheme 1.7-2). Complex **2** was converted to complex **3** with diazomethane. The availability of iminoacyl derivatives from the insertion of isocyanide ligands into Ru–H bonds [4] similarly led to car-



Scheme 1.7-1. Synthesis of the first defined ruthenium(II) metathesis catalyst.

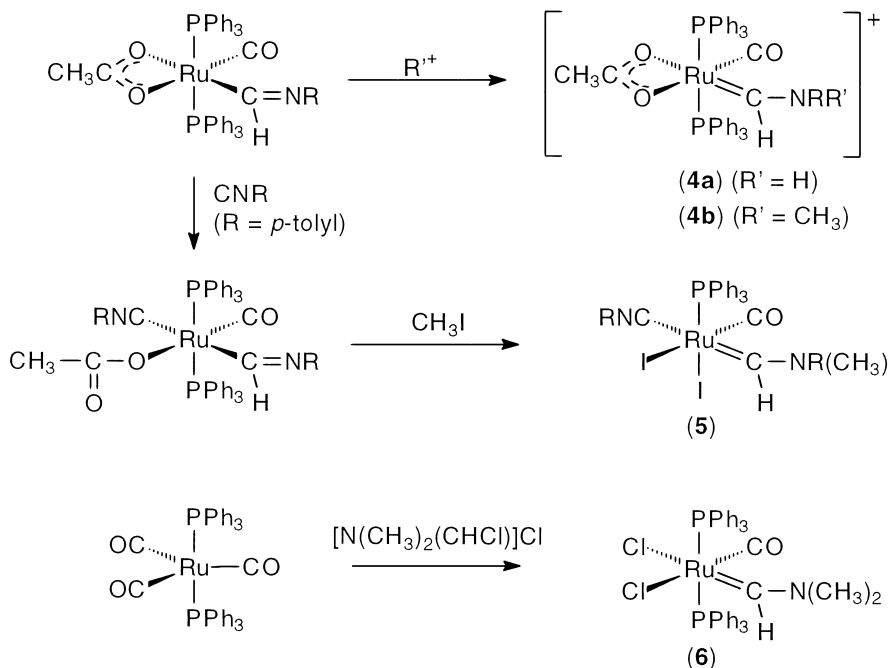


Scheme 1.7-2. The first ruthenium(II) heteroatom-substituted carbene complexes.

bene complexes when protonated (complex 4a) or methylated (complex 4b) at nitrogen as depicted in Scheme 1.7-3 [5]. Crystal structure confirmed the nature of complex 5 [6]. Complex 6, with a closely related carbene ligand, was formed from three-fragment oxidative addition of dimethyl(chloromethylene)ammonium chloride to $\text{Ru}(\text{CO})_3(\text{PPh}_3)_2$ [7].

Throughout the 1970s many ruthenium(II) carbene complexes were reported, but all had one or more stabilizing heteroatoms present on the carbene carbon atom. Many of these contained cyclic ligands, and Scheme 1.7-4 gives a selection of these. Most syntheses relied upon intramolecular alkylation of intermediate acyl (or acyl-related) derivatives. Thus, we see complex 7 produced by a silver-promoted intramolecular alkylation [8], and complex 9 is formed from a related intramolecular alkylation of an intermediate ester derivative formed from complex 8 [9]. A novel disulfur-containing cyclic carbene ligand results from dialkylation of an $\eta^2\text{-CS}_2$ with dibromoethane as shown in the formation of complex 10 [10].

The use of electron-rich olefins for the synthesis of nitrogen-containing cyclic carbene complexes was pioneered by Lappert [7]. The two examples shown in Scheme 1.7-5 involve ruthenium; in complex 11 we see transfer of unaltered carbene ligands, but in complex 12 the introduced *N,N'*-di-*p*-tolylimidazolidin-2-ylidene ligand undergoes an orthometallation reaction. The resulting complex 12 is especially interesting and significant in being the first five-coordinate ruth-



Scheme 1.7.3. Some ruthenium(II) nitrogen-substituted carbene complexes.

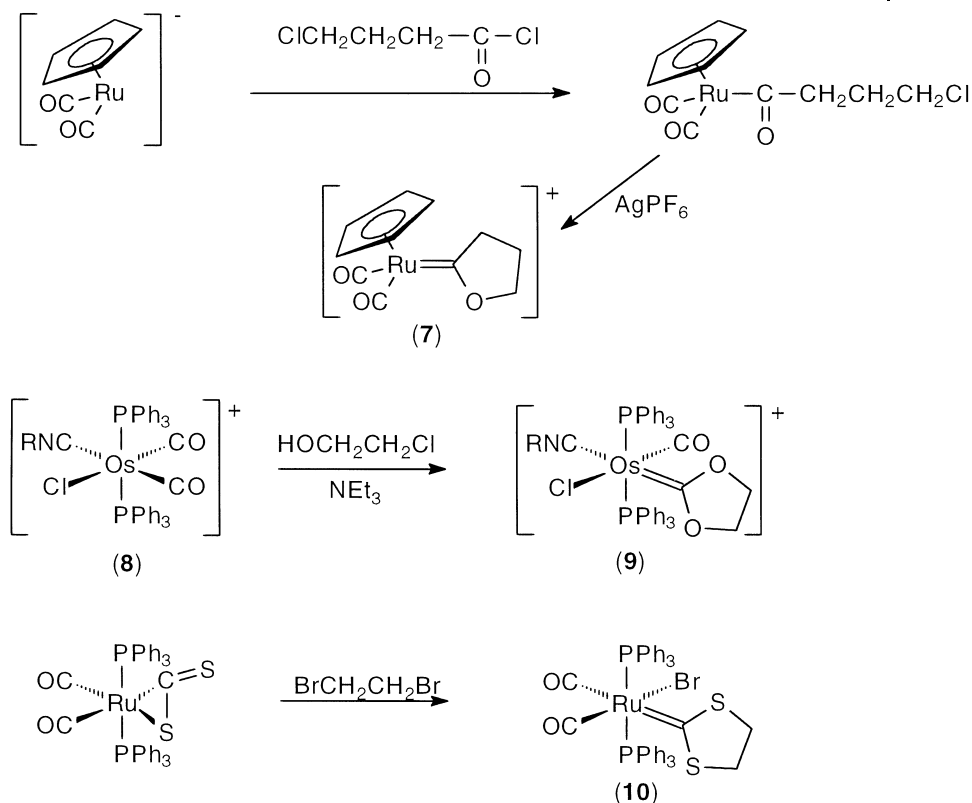
enium(II) carbene complex [11], a feature associated with the family of Grubbs metathesis catalysts. Other organometallic complexes of ruthenium(II) also exhibit five coordination, notably the many compounds of formula $\text{RuRCl}(\text{CO})(\text{PPh}_3)_2$ formed as shown in Scheme 1.7-6 [12]. The geometry of these compounds, like the Grubbs catalyst 1, are tetragonal pyramidal with the vacant coordination site *trans* to the strong *trans* influence ligand, in this case, the σ -bound aryl.

These early studies served to establish that ruthenium formed a wide range of carbene complexes, the reactivity of which followed that found for the Fischer-type complexes.

1.7.3

Ruthenium Methylene Complexes

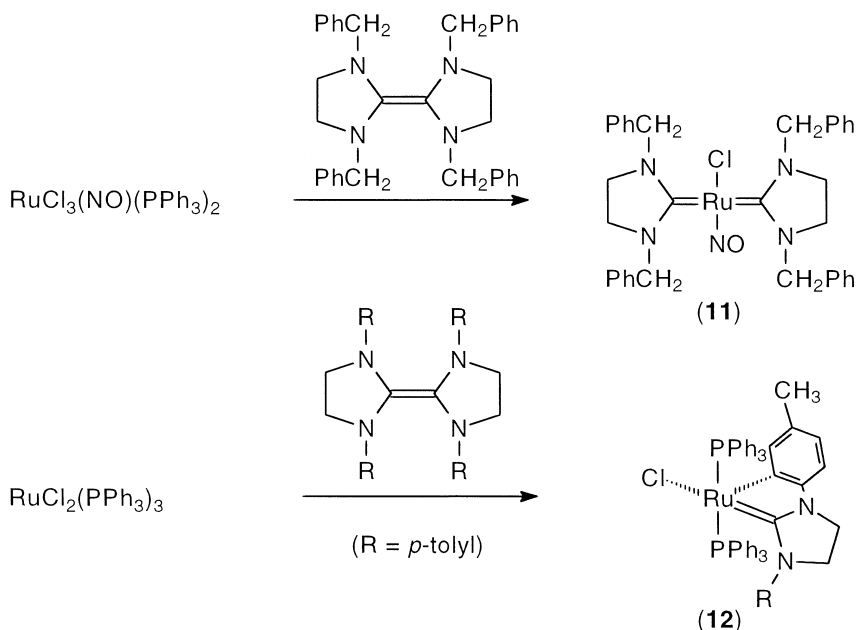
Discoveries of more direct relevance to the Grubbs catalysts were made in the early 1980s. These were alkylidene complexes (carbene complexes without heteroatoms as substituents) and they indeed featured the simplest possible alkylidene ligand, namely, methylene. In Scheme 1.7-7 we see that these resulted from reaction between diazomethane and suitable coordinatively unsaturated (or potentially unsaturated) complexes of ruthenium and osmium (this same route, but involving diazoalkanes and $\text{RuCl}_2(\text{PPh}_3)_3$, was later used to prepare the Grubbs cata-



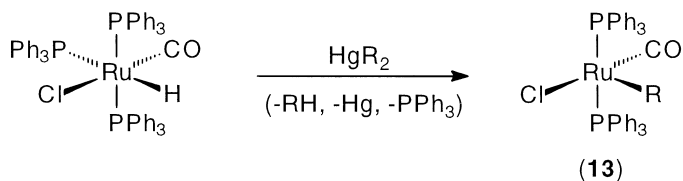
Scheme 1.7-4. Cyclic ruthenium(II) carbene complexes from intramolecular alkylation reactions.

lysts [13]). Crystal structure determinations of the osmium methylene complexes $\text{OsCl}(=\text{CH}_2)(\text{NO})(\text{PPh}_3)_2$ (**14b**) [14] and $\text{OsCl}(\eta^2\text{-C}[\text{O}]\text{o-tolyl})(=\text{CH}_2)(\text{PPh}_3)_2$ (**15b**) [15] provided valuable structural data and placed the formulations of these compounds on a firm footing.

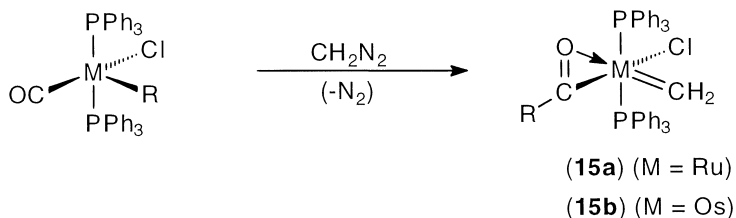
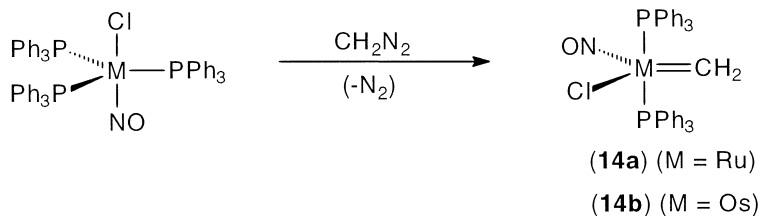
At the time, our motivation for studying these methylene complexes had little to do with olefin metathesis and much more to do with providing well-defined models for the metal-methylene species widely discussed as intermediates in many catalytic procedures, especially in Fischer-Tropsch chemistry. Compounds **14a,b** and **15a,b** exhibit formally different oxidation states, and correspondingly the chemical reactivity they display is different. In Scheme 1.7-8 we see that **14b** (where the osmium is formally $\text{Os}(0)$) undergoes reactions with electrophiles that are effectively additions across the $\text{Os}=\text{C}$ bond [16]. Also, in Scheme 1.7-9 we see that addition of CO to **14b** promotes formation of an η^2 -ketene complex **20** [17], whereas addition of CO to the ruthenium(II) methylene **15a** initiates addition of the acyl oxygen to the electrophilic methylene carbon atom forming a metal-laoxetene ring in complex **21** [18]. Further evidence of the electrophilic nature of the methylene ligand in these ruthenium and osmium complexes with the metal



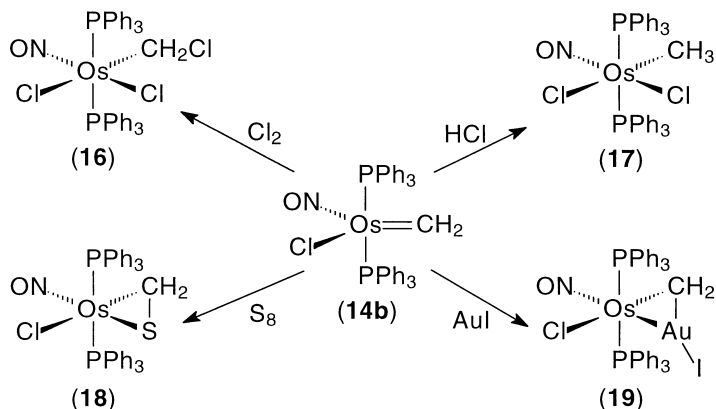
Scheme 1.7-5. Ruthenium(II) carbene complexes from reactions involving electron-rich olefins.



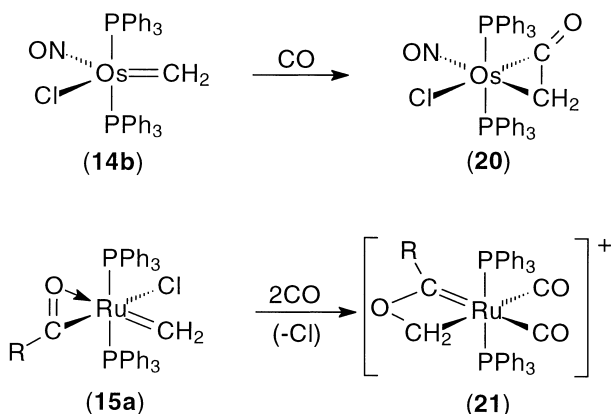
Scheme 1.7-6. Five-coordinate ruthenium(II) complexes.



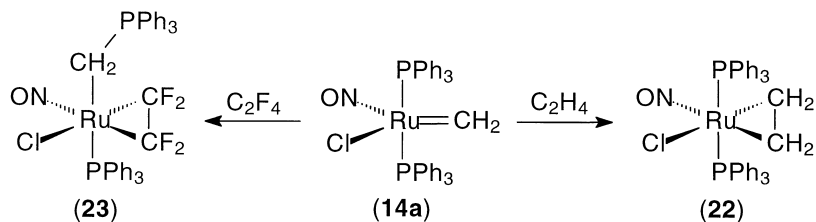
Scheme 1.7-7. Syntheses of ruthenium and osmium methylene complexes.



Scheme 1.7-8. Selected reactions of osmium(0) methylene complex.



Scheme 1.7-9. Differing reactions of zero-valent and divalent methylene complex with CO .



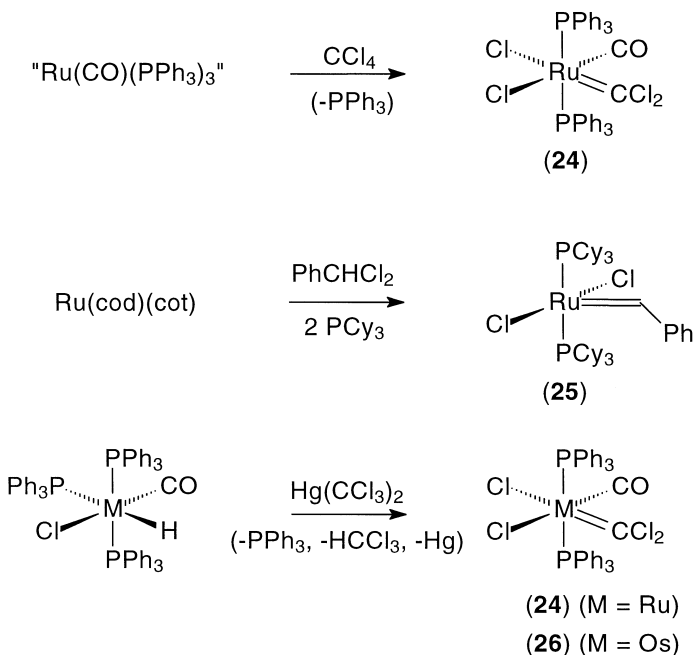
Scheme 1.7-10. Reactions of the zero-valent ruthenium methylene complex with C_2H_4 and C_2F_4 .

in the +2 oxidation state is that after 14a is “oxidized” by addition of C_2F_4 (see Scheme 1.7-10), a triphenylphosphine ligand migrates to methylene, forming the ylid complex 23 [19]. The related reaction of 14a with ethylene results eventually in formation of the $\eta^2\text{-C}_2\text{H}_4$ complex, 22. This observation may be relevant to the ultimate loss of the propagating methylene species in metathesis processes.

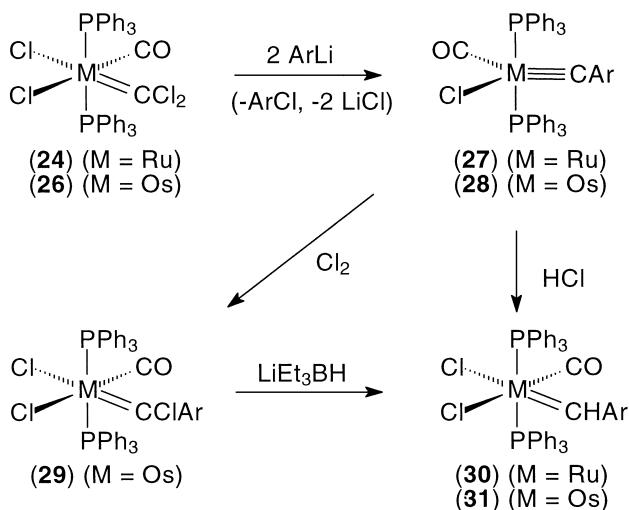
1.7.4

Ruthenium Dihalocarbene Complexes

At first sight, dihalocarbene complexes [20] might seem unrelated to metathesis catalysts. In fact there are several points of contact, a recent one being that metathesis with 1,1-difluoroethylene is an efficient route to difluorocarbene complexes [21]. From the synthetic and structural inorganic chemist's point of view, dihalocarbene complexes are fascinating and versatile complexes, as they provide routes to carbyne complexes, variously substituted carbene complexes, thio-carbonyl complexes, etc. The first ruthenium and osmium examples were provided in 1980 [22]. As we see in Scheme 1.7-11, the ruthenium dichlorocarbene complex, $\text{RuCl}_2(=\text{CCl}_2)(\text{CO})(\text{PPh}_3)_2$ **24**, was first produced [17] by reaction between " $\text{Ru}(\text{CO})(\text{PPh}_3)_3$ " [23] and CCl_4 . Later, the same "three-fragment oxidative addition" utilizing a *gem*-dihalide and a zero-valent ruthenium complex was used as a convenient route to the Grubbs catalyst **25** [24]. A superior route to complex **24** [25] and also the osmium analogue **26** [22] makes use of $\text{Hg}(\text{CCl}_3)_2$. Complexes **24** and **26** give rise to numerous different carbene complexes by substitution reactions at the carbene carbon. Difluorocarbene complexes of ruthenium(II) behave similarly [26]. A reaction of **24** and **26** with aryl lithium reagents leads to carbyne complexes of ruthenium (**27**) and osmium (**28**), as depicted in Scheme 1.7-12 [27]. Reactions of **27** and **28** that are relevant here are that chlorine addition to the $\text{Os}=\text{C}$ bond gives the chlorocarbene complex **29**, and HCl addition gives the ruth-



Scheme 1.7-11. Synthesis of dichlorocarbene complexes of ruthenium(II) and osmium(II).



Scheme 1.7-12. Carbyne and alkylidene complexes of ruthenium(II) and osmium(II).

enium(II) and osmium(II) alkylidene complexes **30** and **31**. It is interesting that the crystal structure of **31** (Ar = Ph) [17] reveals that the chloride *trans* to the =CHPh ligand is almost “ionic” in having an Os–Cl distance of 2.550(3) Å, i.e., the compound is almost an example of a five-coordinate alkylidene complex. The big breakthrough was to come a few years later with Grubbs’ report of a truly five-coordinate simple alkylidene compound, complex **1**, and with it the demonstration that **1** was a highly effective catalyst for many types of alkene metathesis [1].

Acknowledgments

I am very grateful to Bob Grubbs for inviting me to contribute this chapter. It is my hope that the necessarily brief description of ruthenium carbene chemistry up to about 1990, which I have provided, will give a backdrop against which the discovery of the Grubbs catalysts can be better appreciated.

References

- 1 NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.
- 2 FISCHER, E. O.; MAASBÖL, A. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 580.
- 3 GREEN, M. L. H.; MITCHARD, L. C.; SWANWICK, M. G. *J. Chem. Soc. (A)* **1971**, 794.
- 4 CHRISTIAN, D. F.; CLARK, G. R.; ROPER, W. R.; WATERS, J. M.; WHITTLE, K. R. *J. Chem. Soc., Chem. Commun.* **1972**, 458.
- 5 CHRISTIAN, D. F.; ROPER, W. R. *J. Organomet. Chem.* **1974**, *80*, C35.
- 6 CHRISTIAN, D. F.; CLARK, G. R.; ROPER, W. R. *J. Organomet. Chem.* **1974**, *81*, C7.
- 7 LAPPERT, M. F. *J. Organomet. Chem.* **1975**, *100*, 139.
- 8 GAME, C. H.; GREEN, M.; MOSS, J. R.; STONE, F. G. A. *J. Chem. Soc., Dalton Trans.* **1974**, 351.
- 9 GRUNDY, K. R.; ROPER, W. R. *J. Organomet. Chem.* **1976**, *113*, C45.

- 10 COLLINS, T. J.; GRUNDY, K. R.; ROPER, W. R.; WONG, S. F. *J. Organomet. Chem.* **1976**, 107, C37.
- 11 HITCHCOCK, P. B.; LAPPERT, M. F.; PYE, P. L. *J. C. S. Chem. Comm.* **1977**, 196.
- 12 ROPER, W. R.; WRIGHT, L. J. *J. Organomet. Chem.* **1977**, 142, C1; RICKARD, C. E. F.; ROPER, W. R.; TAYLOR, G. E.; WATERS, J. M.; WRIGHT, L. J. *J. Organomet. Chem.* **1990**, 389, 375.
- 13 SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, 107, 2179; SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, 118, 100.
- 14 HILL, A. F.; ROPER, W. R.; WATERS, J. M.; WRIGHT, A. H. *J. Am. Chem. Soc.* **1983**, 105, 5939.
- 15 BOHLE, D. S.; CLARK, G. R.; RICKARD, C. E. F.; ROPER, W. R.; SHEPARD, W. E. B.; WRIGHT, L. J. *J. Chem. Soc., Chem. Commun.* **1987**, 563.
- 16 ROPER, W. R. in *Advances in Metal Carbene Chemistry*, ed. U. SCHUBERT, Kluwer Academic Publishers, Dordrecht, **1989**, p. 27.
- 17 ROPER, W. R. *J. Organomet. Chem.* **1986**, 300, 167.
- 18 BOHLE, D. S.; CLARK, G. R.; RICKARD, C. E. F.; ROPER, W. R.; WRIGHT, L. J. *J. Organomet. Chem.* **1988**, 358, 411.
- 19 BURRELL, A. K.; CLARK, G. R.; RICKARD, C. E. F.; ROPER, W. R.; WRIGHT, A. H. *J. Chem. Soc. Dalton Trans.* **1991**, 609.
- 20 BROTHERS, P. J.; ROPER, W. R. *Chem. Rev.* **1988**, 88, 1293.
- 21 TRNKA, T. M.; DAY, M. W.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2001**, 40, 3441.
- 22 CLARK, G. R.; MARSDEN, K.; ROPER, W. R.; WRIGHT, L. J. *J. Am. Chem. Soc.* **1980**, 102, 1206.
- 23 ROPER, W. R.; WRIGHT, L. J. *J. Organomet. Chem.* **1982**, 234, C5.
- 24 BELDERRAIN, T. R.; GRUBBS, R. H. *Organometallics* **1997**, 16, 4001.
- 25 ROPER, W. R.; WRIGHT, A. H. *J. Organomet. Chem.* **1982**, 233, C59.
- 26 CLARK, G. R.; HOSKINS, S. F.; ROPER, W. R. *J. Organomet. Chem.* **1982**, 234, C9.
- 27 CLARK, G. R.; MARSDEN, K.; ROPER, W. R.; WRIGHT, L. J. *J. Am. Chem. Soc.* **1980**, 102, 6570.

1.8

Synthesis of Rhodium and Ruthenium Carbene Complexes with a 16-Electron Count

Helmut Werner and Justin Wolf

1.8.1

Introduction

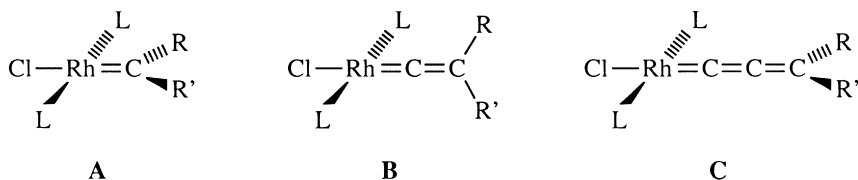
Although the isolation and structural characterization of the first transition metal carbene complex dates back to 1964 [1], the chemistry of this class of compounds has remained one of the most attractive fields of research ever since [2]. Due to the preferred reactivity of the complexes of the general composition $[M(=CRR')(L)_n]$ to either nucleophiles or to electrophiles, it is nowadays common to divide transition metal carbenes into those of the Fischer type and the Schrock type, thereby giving credit to the pioneers of this field [3, 4]. Prominent examples of Fischer-type carbenes contain an alkoxy or dialkyl amino substituent at the carbene carbon atom, while Schrock-type carbenes possess CH_2 , CHR , or CR_2 units (R = alkyl or aryl) coordinated to the metal center.

There are two well-known routes to prepare a transition metal carbene with a CH_2 , CHR , or CR_2 ligand. The first, developed by Schrock [4], commonly uses a metal halide compound as the starting material, which is transformed via an alkyl intermediate into a metal carbene by abstraction of a proton. The second method, mainly developed by Herrmann [5] and Roper [6], employs diazomethane and its derivatives as precursors and in the coordination sphere generates either thermally or photochemically the carbene ligand by elimination of N_2 .

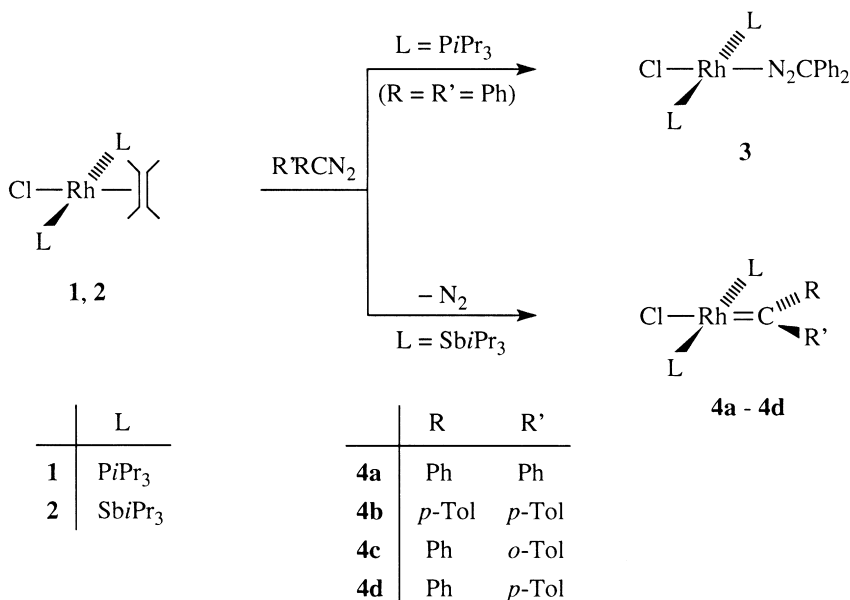
1.8.2

Rhodium(I) Carbenes from Diazoalkanes

Beginning in the early 1990s, our group attempted to use the diazoalkane methodology in order to obtain rhodium carbenes of type **A** (Scheme 1.8-1). After we had succeeded in the 1980s in the synthesis of the related rhodium vinylidenes and allenylidenes of type **B** and **C** [7, 8], and after we learned that these complexes undergo unusual addition and insertion reactions [9], we also became interested in preparing the parent compounds in this series and in finding out what their reactivity is. While neither $[RhCl(PiPr_3)_2]_2$ nor *trans*- $[RhCl(C_2H_4)(PiPr_3)_2]$ (which both



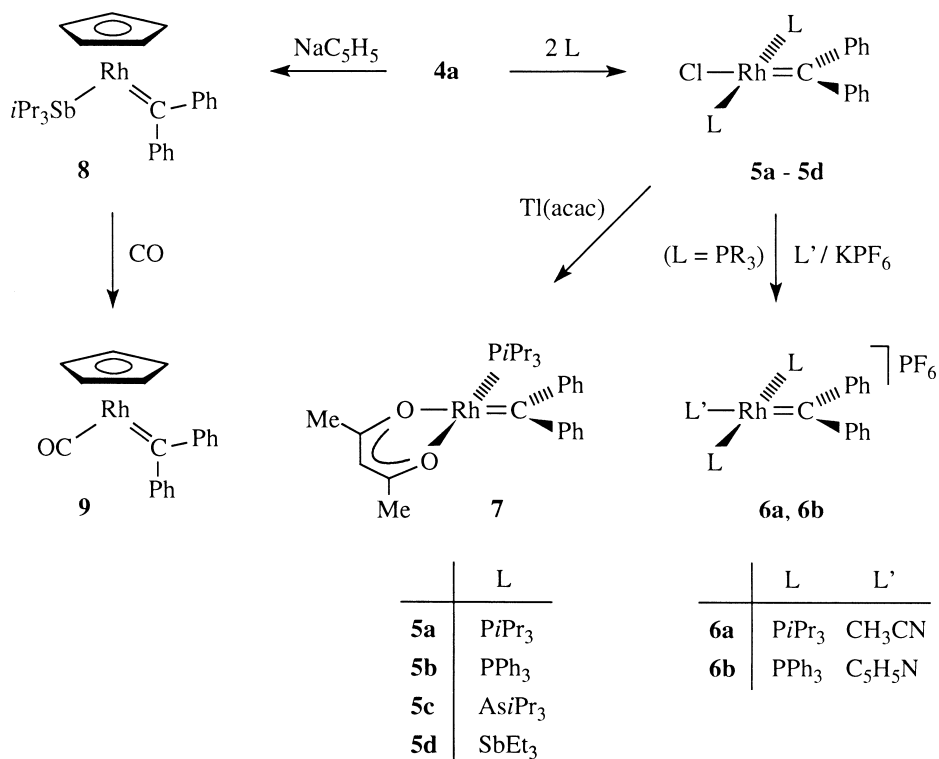
Scheme 1.8-1. Homologous series of 16-electron rhodium(I) carbenes, vinylidenes, and allenylidenes (L = PiPr_3).



Scheme 1.8-2. Products of the reactions of structurally related ethenerhododium(I) complexes with diaryldiazomethanes (Ph = C_6H_5 , *p*-Tol = 4-Me C_6H_4 , *o*-Tol = 2-Me C_6H_4).

can be used to obtain metallacumulenes of type **B** and **C**) reacted with PhCHN_2 or Ph_2CN_2 to give a metal carbene [10], we attempted to modify the coordination sphere in the hope of generating a more reactive rhodium species.

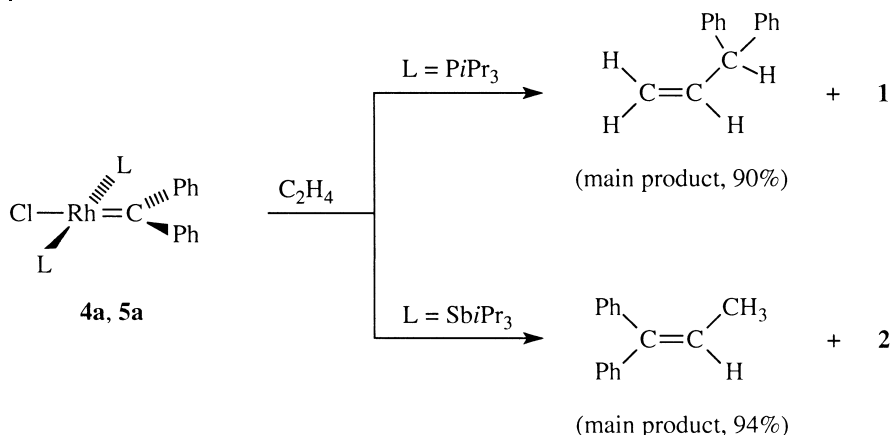
The key to success was to use the analogous bis(triisopropylstibine) complex *trans*- $[\text{RhCl}(\text{C}_2\text{H}_4)(\text{SbiPr}_3)_2]$ (**2**), rather than *trans*- $[\text{RhCl}(\text{C}_2\text{H}_4)(\text{PiPr}_3)_2]$ (**1**), as the starting material. It reacts with diaryldiazoalkanes under mild conditions (pentane, room temperature) to give the rhodium carbenes **4a–4d** in excellent yields via displacement of ethene and elimination of N_2 (Scheme 1.8-2) [11]. In contrast, attempts to prepare *trans*- $[\text{RhCl}(=\text{CH}_2)(\text{SbiPr}_3)_2]$ and *trans*- $[\text{RhCl}(=\text{CHPh})(\text{SbiPr}_3)_2]$ in the same way failed. Compounds **4a–4d** are remarkably stable and can be used for the preparation of a variety of other rhodium carbenes. This is exemplified for **4a** in Scheme 1.8-3 [11, 12]. Among the products obtained from **4a**, the bis(triisopropylphosphine) complex **5a** is particularly noteworthy insofar as it was



Scheme 1.8-3. Rhodium(I) carbenes with a 16-electron count (**5a–5d**, **6a**, **6b**, **7**) and an 18-electron count (**8**, **9**) prepared from **4a** as starting material.

not only the original target of our studies but it is also not the product of the thermal reaction of the diphenyldiazomethane compound **3**. In this case, instead of **5a** the dinitrogen derivative $\text{trans}[\text{RhCl}(\text{N}_2)(\text{PiPr}_3)_2]$ is formed [13]. We note that quite recently Milstein et al. found that the phenylcarbene complex $\text{trans}[\text{RhCl}(\text{=CHPh})(\text{PiPr}_3)_2]$, for which the bis(stibine) analogue does not exist, can be obtained from $[\text{RhCl}(\text{PiPr}_3)_2]_2$ and the sulfur ylide Ph_2SCHPh in toluene at -30°C . The complex is moderately stable and decomposes at room temperature within 3–4 days [14].

Although the neutral and cationic rhodium carbenes **4a**, **5a–5d** [11], **6a**, **6b**, and **7** [15], similar to the Grubbs catalyst $[\text{RuCl}_2(\text{=CHPh})(\text{PCy}_3)_2]$, possess a 16-electron count, they are not catalytically active in olefin metathesis. However, they react smoothly with ethene to afford a mixture of products, each of which is built up by one CPh_2 unit and one or two C_2H_4 molecules. There is a dramatic influence of the apparently “innocent” ligands L on the structure of the main component (a 1:1 adduct of C_2H_4 and CPh_2), which, using **4a** and **5a** as examples, is illustrated in Scheme 1.8-4 [11]. The remarkable facet of these results is that only traces of the corresponding cyclic isomer 1.1-diphenylcyclopropane are formed, the latter being



Scheme 1.8-4. Formation of isomeric olefins from the reactions of the structurally related rhodium(I) carbenes **4a** and **5a** with ethene.

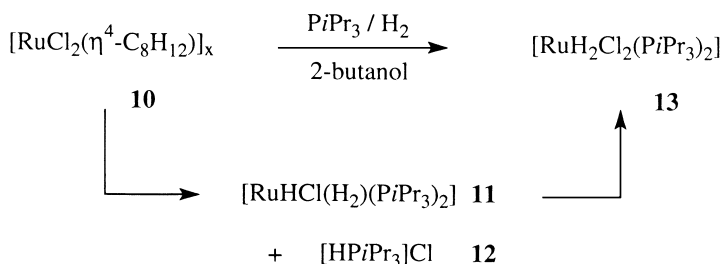
the major product of the reaction of C_2H_4 and Ph_2CN_2 catalyzed by either $[\text{Rh}_2(\mu\text{-O}_2\text{CMe})_4]$ and related rhodium(II) derivatives [16] or $\text{cis-}[\text{Rh}(\text{acetone})_2(\text{PiPr}_3)_2]\text{PF}_6$ [17], respectively. It is even more noteworthy that under the various conditions applied for the reactions of **4a** and **5a** with C_2H_4 , no 1,1-diphenylethene, being the product of olefin metathesis, could be detected.

1.8.3

Ruthenium(II) Carbenes and Vinylidenes from Terminal Alkynes

After we learned that Peter Schwab (who pioneered the research on rhodium(I) carbenes in our laboratory) successfully applied the diazoalkane route to prepare the Grubbs catalyst $[\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2]$ [18], we concentrated our efforts on the synthesis of corresponding five-coordinate ruthenium(II) vinylidenes $[\text{RuCl}_2(=\text{C}=\text{CHR})(\text{PR}'_3)_2]$ ($\text{R} = \text{H}$, alkyl, aryl; $\text{R}' = i\text{Pr}$, Cy). In earlier work, concerned with the reactivity of dichlororuthenium(II) complexes containing hemilabile, chelating phosphines such as $i\text{Pr}_2\text{PCH}_2\text{CH}_2\text{OMe}$ and $i\text{Pr}_2\text{PCH}_2\text{CO}_2\text{Me}$ as ligands, it was shown that these compounds afford in the presence of 1-alkynes six-coordinate ruthenium(II) vinylidenes $[\text{RuCl}_2(=\text{C}=\text{CHR})(i\text{Pr}_2\text{PCH}_2\text{CH}_2\text{OMe-}\kappa\text{-P})(i\text{Pr}_2\text{PCH}_2\text{-CH}_2\text{OMe-}\kappa^2\text{-P,O})]$ and $[\text{RuCl}_2(=\text{C}=\text{CHR})(i\text{Pr}_2\text{PCH}_2\text{CO}_2\text{Me-}\kappa\text{-P})\{i\text{Pr}_2\text{PCH}_2\text{C(OMe)O-}\kappa^2\text{-P,O}\}]$ in good to excellent yields [19].

For the preparation of the five-coordinate complexes $[\text{RuCl}_2(=\text{C}=\text{CHR})(\text{PiPr}_3)_2]$, we first considered a dichloro compound such as $[\text{RuCl}_2(\text{PiPr}_3)_3]$ or $[\text{RuCl}_2(\text{PiPr}_3)_2]_n$ as an appropriate starting material. However, all attempts to obtain a ruthenium(II) species of this type using either $\text{RuCl}_3\cdot\text{aq}$ or $[\text{RuCl}_2(\text{PPh}_3)_3]$ as precursors failed. The better choice was to use the (probably polymeric) 1,5-cyclooctadiene derivative $[\text{RuCl}_2(\eta^4\text{-C}_8\text{H}_{12})]_x$ (**10**) [20]. Treating a suspension of **10** in 2-butanol with 3 equivalents of PiPr_3 in the presence of H_2 afforded a red

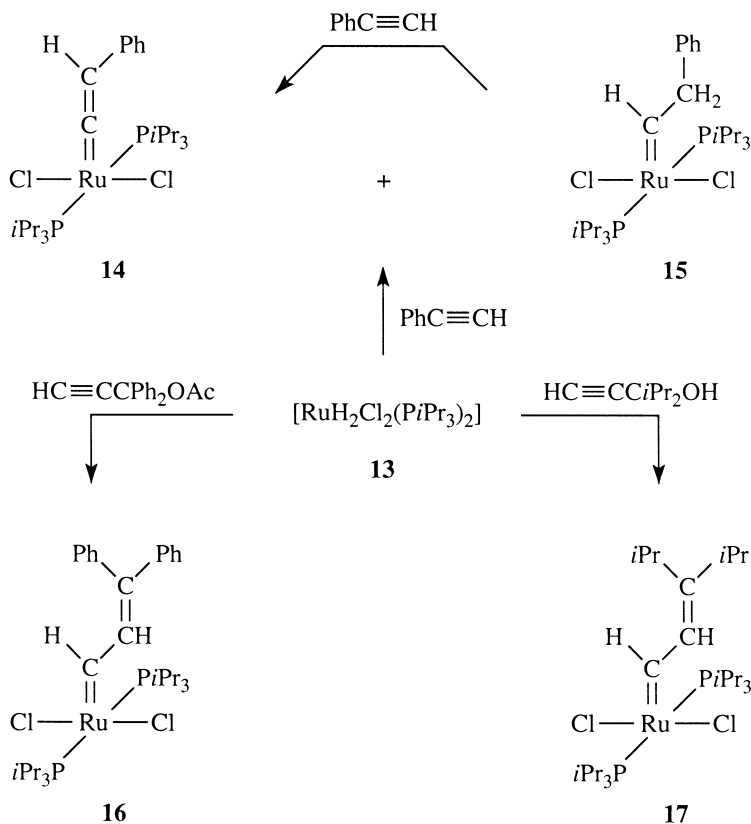


Scheme 1.8-5. Formation of the dihydridoruthenium(IV) complex **13** via the hydrido(dihydrogen)ruthenium(II) compound **11** as an intermediate.

solution that contained the hydrido(dihydrogen) complex **11** (Scheme 1.8-5). This compound, originally prepared by Chaudret et al. from $[\text{Ru}(\eta^4\text{-C}_8\text{H}_{12})(\eta^6\text{-C}_8\text{H}_{10})]$, PiPr_3 and CHCl_3 under H_2 pressure [21], reacts with the phosphonium salt **12** (formed as a byproduct in the reaction of **10**) to give the ruthenium(IV) complex **13** in almost quantitative yield [20]. The X-ray crystal structure analysis of this unusual molecule, having a 16-electron count, revealed that the geometry is best described as a somewhat distorted variant of a D_{4d} square antiprism with the two vacant coordination sites in alternate positions at one square base of this polyhedron. The other square base is made up by the two phosphorus atoms and the two hydrido ligands, the position of which has been located in a difference Fourier synthesis [20]. The hydrido(dihydrogen) compound **11** can be isolated analytically purely if the reaction of **10** with PiPr_3 and H_2 in 2-butanol is carried out in the presence of NEt_3 as a base.

The reaction of the ruthenium(IV) complex **13** with phenylacetylene yields a mixture of two products, **14** and **15**, of which the ruthenium vinylidene **14** is the dominating species [20]. It is exclusively formed if the initially generated reaction mixture, after removal of the secondary alcohol, is treated again with $\text{PhC}\equiv\text{CH}$ and heated to 80°C for a short period of time. The corresponding benzylcarbene compound **15** can be prepared (and isolated in 67% yield) if the solution containing both **11** and **12** (see Scheme 1.8-5) is treated with 2 equivalents of phenylacetylene at -78°C [20a]. The molecular structure of **15** is quite similar to that of the vinylcarbene complex $[\text{RuCl}_2(=\text{CHCH}=\text{CPh}_2)(\text{PCy}_3)_2]$ [22] and corresponds to a distorted square pyramid. In the same way as described for **15**, the methylcarbene-ruthenium(II) compound $[\text{RuCl}_2(=\text{CHCH}_3)(\text{PiPr}_3)_2]$ has been prepared from the mixture of **11/12** and acetylene at room temperature [20a].

The dichlorodihydrido complex **13** reacts not only with phenylacetylene but also with propargylic alcohols and derivatives thereof. The results are summarized in Scheme 1.8-6. The formation of **16** (a compound originally prepared by Grubbs et al. from $[\text{RuCl}_2(\text{PPh}_3)_3]$ and 1.1-diphenylcyclopropene followed by ligand exchange of PPh_3 for PiPr_3 [22]) is noteworthy insofar as the corresponding alcohol $\text{HC}\equiv\text{CCPh}_2\text{OH}$ usually behaves as a source for an allenylidene but not a vinylcarbene unit [19b,c, 23]. From a mechanistic point of view, the formation of **16** and **17** from **13** can be understood best if it is assumed that, analogous

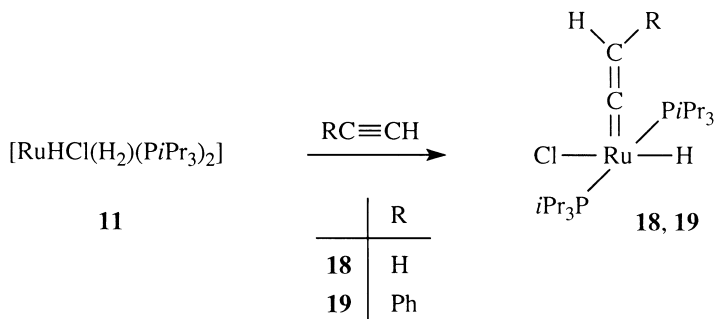


Scheme 1.8-6. Reactions of the dihydridoruthenium(IV) complex **13** with terminal alkynes [Ac = CH₃C(=O)].

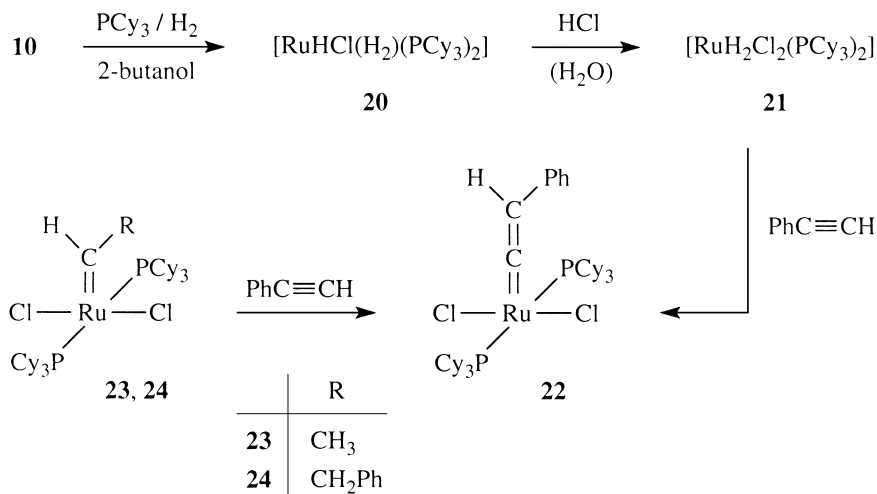
to the course of the reaction of **13** with PhC≡CH, a hydrido(vinyl) species [RuHCl₂(CH=CHCR₂OR')(PiPr₃)₂] (R' = H, Ac) is generated as an intermediate that affords the product by elimination of HOR'.

Under conditions similar to those used for the reactions of **13**, the ruthenium(II) compound **11** reacts with acetylene and phenylacetylene to give the hydrido(vinylidene) complexes **18** and **19**, respectively (Scheme 1.8-7). The counterparts with PtBu₂Me as phosphine ligand and the compositions [RuHCl(=C=CHPh)(L)₂] and [RuHCl(=C=CHSiMe₃)(L)₂] were prepared by Caulton et al. from [RuHCl(H₂)(L)₂] (L = PtBu₂Me) as the precursor [24]. Since **18** and **19** are readily soluble in organic solvents, including pentane and hexane, the isolated yield for both compounds was only about 40% [20b].

The analogues of **11** and **13** with two PCy₃ instead of two PiPr₃ ligands are also accessible from the 1,5-cyclooctadiene derivative **10** (Scheme 1.8-8) [20b]. Similar to **11**, the hydrido(dihydrogen) complex **20** was first prepared by Chaudret et al. using the ruthenium(0) compound [Ru(η⁴-C₈H₁₂)(η⁶-C₈H₁₀)] as the starting material [21]. Parallel to our work, Grubbs et al. published an experimental procedure

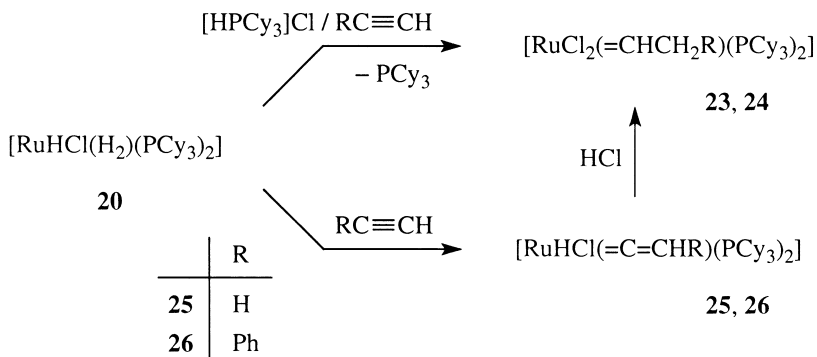


Scheme 1.8-7. Preparation of the hydrido(vinylidene)ruthenium-(II) complexes **18** and **19** from the hydrido(dihydrogen) compound **11** as precursor.



Scheme 1.8-8. Preparative routes to monohydrido, dihydrido, and vinylidene ruthenium complexes with $[Ru(PCy_3)_2]$ as building block.

for **20** that also used **10** as the precursor [25]. In contrast to the conversion of **11** to **13** (see Scheme 1.8-5), the preparation of **21** is best done by treatment of **20** in CH_2Cl_2 with an aqueous solution of HCl at room temperature [20b]. The subsequent reaction of **21** with phenylacetylene in the molar ratio of 1:10 gave the vinylidene complex **22** in 67% isolated yield. Alternatively, **22** can be prepared from **23** or **24** (Scheme 1.8-9) and phenylacetylene by displacing the carbene ligand (see, for comparison, the conversion of **15** to **14** mentioned in Scheme 1.8-6) [20] and, as Katayama and Ozawa have shown [26], from $[RuCl_2(p\text{-cymene})]_2$, PCy_3 , and phenylacetylene in toluene at 80 °C. By using this route, the *t*-butylvinylidene and ferrocenylvinylidene compounds $[RuCl_2(=C=CHR)(PR'_3)_2]$ ($R = tBu, Fc$; $R' = iPr, Cy$) were also obtained [26].

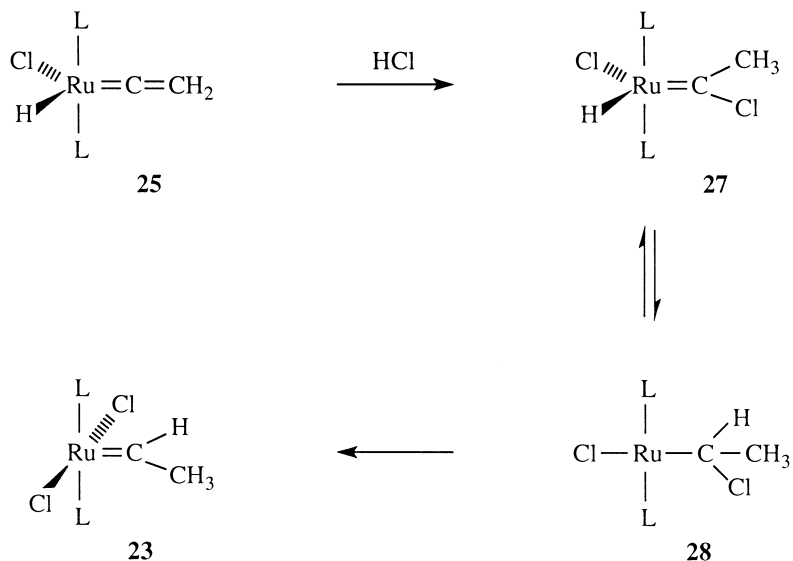


Scheme 1.8-9. Preparation of both carbene and hydrido(vinylidene) ruthenium(II) complexes from the hydrido(dihydrogen) compound **20** as precursor.

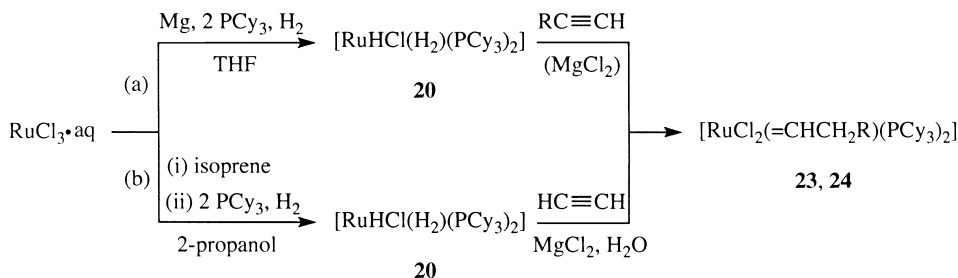
The hydrido(dihydrogen) complex **20** is an excellent starting material for the preparation of ruthenium carbenes of the Grubbs type. Independent of work done in the Grubbs group [25, 27], we found that **20** reacts with acetylene and phenylacetylene in CH_2Cl_2 in the presence of 1 equivalent of $[\text{HPCy}_3]\text{Cl}$ to give the compounds **23** and **24** in excellent yields [28]. Without $[\text{HPCy}_3]\text{Cl}$, the reaction of **20** with $\text{RC}\equiv\text{CH}$ ($\text{R} = \text{H}, \text{Ph}$) leads to the formation of the hydrido(vinylidene) complexes **25** and **26** (Scheme 1.8-9). Both **25** and **26** slowly decompose in benzene or dichloromethane and are less stable than the triisopropylphosphine counterparts **18** and **19**. As anticipated, treatment of **25** and **26** with either $[\text{HPCy}_3]\text{Cl}$ or HCl (in C_6H_6) affords the ruthenium carbenes **23** and **24** almost quantitatively [28, 29]. It should be noted that, regarding the reactivity of **20** toward terminal alkynes and HCl , there is an interesting interplay insofar as, by reversing the two reaction steps, either five-coordinate ruthenium carbenes or vinylidenes can be obtained. Thus, treatment of **20** first with $\text{RC}\equiv\text{CH}$ and then with HCl yields the carbenes **23** and **24** (Scheme 1.8-9), while using HCl first and phenylacetylene second gives the vinylidene **22**.

The postulated mechanism for the conversion of **25** to **23** is shown in Scheme 1.8-10. We assume that in the initial step HCl attacks the $\text{C}=\text{C}$ bond of the vinylidene ligand to generate **27**, which is transferred into the second intermediate **28** by inserting the carbene into the $\text{Ru}-\text{H}$ bond. The final step consists of an $\alpha\text{-Cl}$ shift from carbon to ruthenium to afford the product. We note that 14-electron species such as **28** were also discussed as possible intermediates in the reaction of **20** with vinylchlorides [25] and, moreover, that the reaction of **25** with DCl exclusively gives the compound $[\text{RuCl}_2(=\text{CHCH}_2\text{D})(\text{PCy}_3)_2]$, which is in agreement with the mechanistic model [28].

Attempts to isolate the intermediate **27** (see Scheme 1.8-10) led to an unexpected result. We found that a complete conversion of **25** to **23** also takes place if the starting material is treated with MgCl_2 in the presence of water. This observation led to the development of a simple one-pot synthesis of **23** [28]. Following this procedure, commercial $\text{RuCl}_3\cdot\text{aq}$ is treated with PCy_3 and then reduced with



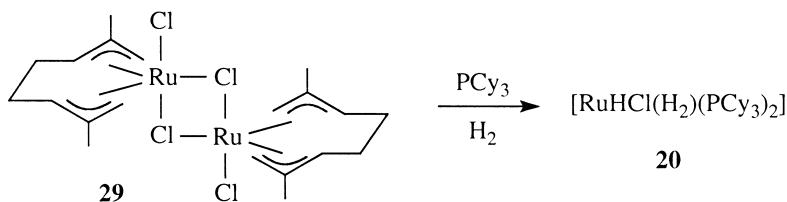
Scheme 1.8-10. Postulated mechanism for the reaction of the hydrido(vinylidene) complex **25** with HCl to give **23** ($\text{L} = \text{PCy}_3$).



Scheme 1.8-11. Two preparative routes to prepare the ruthenium carbenes **23** and **24** used as catalysts for ROMP and RCM.

$\text{Mg}/1.2\text{-C}_2\text{H}_4\text{Cl}_2$ in THF at $60\text{--}85^\circ\text{C}$ under a hydrogen atmosphere to the hydrido(dihydrogen) compound **20**. After the reaction mixture is cooled to -40°C , 2 equivalents of acetylene and a small amount of water are added. While warming the solution to room temperature, the carbene complex **23** is formed and, after removal of the solvent and extraction of the residue with pentane, isolated in about 75% yield. In the same way, but by using only 1 equivalent of $\text{PhC}\equiv\text{CH}$, the benzylcarbene derivative **24** is obtained. Both **23** and **24** show almost the same activity as the Grubbs catalyst $[\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2]$ in olefin metathesis (ring-opening metathesis polymerization [ROMP] and ring-closing metathesis [RCM]) and are now prepared in an industrial research lab in 100-g quantities [30].

Recently, the preparative route (a) to give **23** and **24** was even more simplified (see Scheme 1.8-11). Instead of using $\text{Mg}/1.2\text{-C}_2\text{H}_4\text{Cl}_2$ and THF as solvent, we



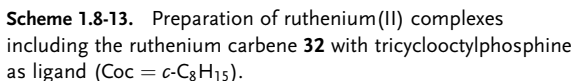
Scheme 1.8-12. Preparation of the hydrido(dihydrogen) compound **20** from the dinuclear octadienyldruthenium(IV) complex as precursor.

used isoprene and 2-propanol as substrates to convert $\text{RuCl}_3 \cdot \text{aq}$ into a more reactive intermediate. This intermediate probably is the dinuclear compound $[\text{RuCl}(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})]_2$ (**29**) (Scheme 1.8-12), which was first reported by Porri et al. in 1965 [31] and in subsequent studies was used as catalyst for olefin metathesis [32]. To support our proposal, we showed that treatment of a suspension of **29** in 2-propanol with PCy_3 under dihydrogen gives the hydrido(dihydrogen) complex **20** in 92% isolated yield [33]. According to route (b), the intermediate **20** reacts with acetylene in the presence of MgCl_2 and water to afford **23** in about 80% yield [29]. We note that with **29** as the starting material, in a stepwise fashion, a cationic ruthenium carbene $[\text{RuCl}(\text{=CHCH}_3)(\text{PF}_3)(\text{PCy}_3)_2]\text{BF}_4$ containing PF_3 as an additional ligand also has been prepared [33].

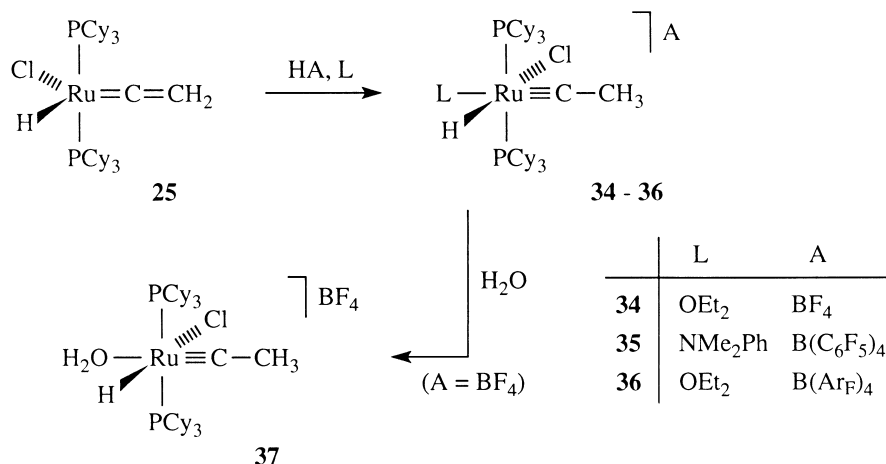
In order to find an even better application profile for the ruthenium carbenes in olefin metathesis, we also exchanged the chlorides in compound **23** for other anionic ligands. Treatment of **25** (see Scheme 1.8-9) with $\text{CF}_3\text{CO}_2\text{H}$ and HCN afforded the complexes $[\text{RuCl}(\text{X})(\text{=CHCH}_3)(\text{PCy}_3)_2]$ ($\text{X} = \text{CF}_3\text{CO}_2, \text{CN}$) [**28**, **29**] which, however, are rather labile and slowly decompose (or disproportionate) in solution. The bis(trifluoroacetato) derivative $[\text{Ru}(\kappa^1\text{-O}_2\text{CCF}_3)_2(\text{=CHCH}_3)(\text{PCy}_3)_2]$ was obtained upon addition of $\text{CF}_3\text{CO}_2\text{H}$ to $[\text{RuH}(\kappa^1\text{-O}_2\text{CCF}_3)(\text{=C=CH}_2)(\text{PCy}_3)_2]$, the latter being generated from **25** and $\text{CF}_3\text{CO}_2\text{K}$ [29]. All these new carbene complexes (including the diiodo compound $[\text{RuI}_2(\text{=CHCH}_3)(\text{PCy}_3)_2]$, prepared by salt metathesis from **23** and excess NaI) are catalytically less active than the parent dichloro derivative in ROMP of norbornene and *cis*-cyclooctene, respectively [29].

Following the assumption [18, 34] that increasing the size of the tertiary phosphines in compounds of the general composition $[\text{RuCl}_2(\text{=CHR})(\text{PR}'_3)_2]$ should result in increased catalytic activity, the formerly unknown tricyclooctylphosphine PCoc_3 as well as the corresponding hydrido(vinylidene) and methylcarbene ruthenium complexes **30**, **32**, and **33** have been prepared [34]. The results are summarized in Scheme 1.8-13. With regard to the reactivity of **31–33**, the general (disappointing) conclusion is that they are poor catalysts for ROMP of *cis*-cyclooctene or dicyclopentadiene and, in the presence of HBF_4 , for cross-olefin metathesis of cyclopentene with methyl acrylate [34].

An active catalyst for the latter reaction was discovered on a different pathway. Taking into consideration that the active species in olefin metathesis reactions catalyzed by $[\text{RuCl}_2(\text{=CHR})(\text{PCy}_3)_2]$ probably is the corresponding 14-electron molecule $[\text{RuCl}_2(\text{=CHR})(\text{PCy}_3)]$ [35], we attempted to prepare a related



The cationic carbyne(hydrido) compounds **34–37** are highly efficient catalysts for olefin metathesis. Detailed investigations have been carried out in our lab with **34**, which catalyzes ROMP of cyclic olefins such as cyclopentene, cyclooctene, 1,5-cyclooctadiene, dicyclopentadiene, and oxanorbornene derivatives even more effec-

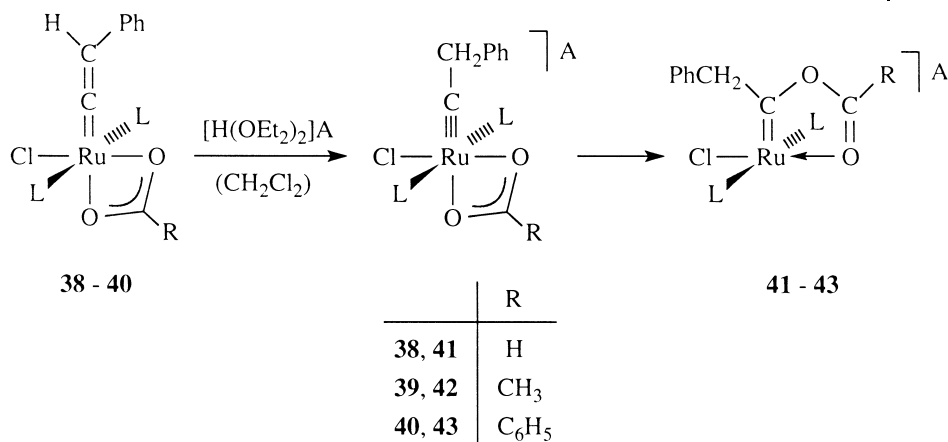


Scheme 1.8-14. Preparation of cationic carbyne(hydrido)-ruthenium(II) complexes by protonation of hydrido(vinylidene) precursors [Ar_F = 3,5-C₆H₃(CF₃)₂].

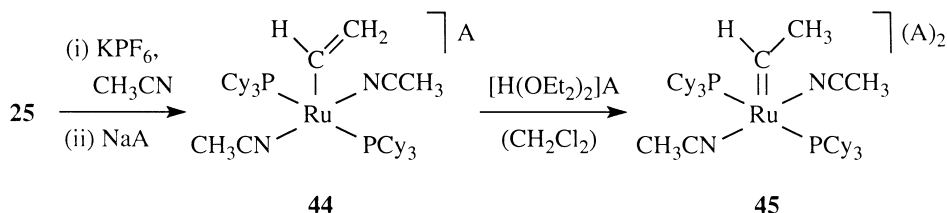
tively than the ruthenium carbene [RuCl₂(=CHPh)(PCy₃)₂] [29, 36]. A comparison experiment revealed that ROMP of cyclooctene (room temperature, $c_{\text{cat}} = 10^{-3}$ M, time: 3 min, yield 90%) with **34** as the catalyst is about 20 times faster than with the Grubbs complex. The amount of *trans*-configured double bonds in the polymer is 76%.

Even more significant than the activity in ROMP, however, is the ability of **34–37** to catalyze the cross-olefin metathesis of cyclopentene with methyl acrylate [36]. Hereby, a mixture of the first members ($n = 1–3$) of the homologous series of unsaturated esters (CH₂=CHCH₂CH₂CH₂CH)_{*n*}CHCO₂Me is formed with a selectivity of 50%, 40%, and 10%, respectively. By using 0.552 mol methyl acrylate, 0.045 mol cyclopentene, and 0.077 mmol of **34** as a catalyst, the yield of unsaturated esters is 2.5 g [29]. It is interesting to note that the ruthenium carbenes **23**, **24**, and [RuCl₂(=CHPh)(PCy₃)₂] are catalytically inactive in this process.

Because, despite their efficiency, the compounds **34–37** are rather labile and decompose in solution within 20 min at room temperature, a variety of more stable ruthenium carbynes were prepared from different ruthenium vinylidenes as precursors. With Brookhart's acid [H(OEt₂)₂][B{C₆H₃(CF₃)₂}]₄, compounds of the general composition [RuCl₂(=C=CHR)(PR'₃)₂] (R = *t*Bu, Ph; R' = *i*Pr, Cy), [RuCl(κ²-O₂CR)(=C=CHPh)(PiPr₃)₂] (R = H, CH₃, CH₂F, CHF₂, C₆H₅, 4-C₆H₄NO₂, 2-C₆H₄NO₂, C₆F₅, 2,4-C₆H₃(NO₂)₂), and [Ru(κ¹-O₂CR)(κ²-O₂CR)(=C=CHPh)(PiPr₃)₂] (R = CHF₂, CF₃) were protonated and in several cases gave stable five- or six-coordinate carbyne complexes in excellent yields [39]. Quite remarkably, the protonation of the carboxylato derivatives **38–40** led to the formation of the cyclic carbenes **41–43**, which are generated via nucleophilic attack of the carboxylato ligand to a cationic carbyneruthenium intermediate (Scheme 1.8-15). Related six-coordinate cyclic carbene complexes were obtained



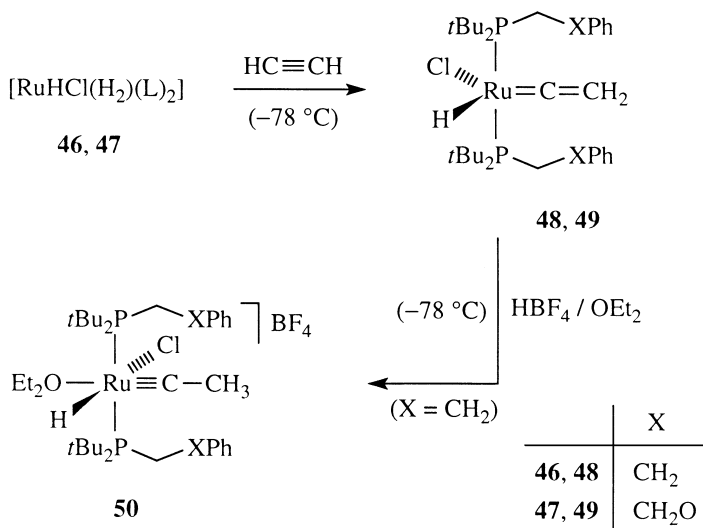
Scheme 1.8-15. Preparation of cationic five-coordinate cyclic ruthenium carbenes by protonation of six-coordinate ruthenium vinylidenes via ruthenium carbynes as intermediates (L = $\text{P}i\text{Pr}_3$; A = $[\text{B}\{\text{C}_6\text{H}_3(\text{CF}_3)_2\}_4]$).



Scheme 1.8-16. Preparation of a dicationic five-coordinate ruthenium carbene by protonation of a vinylruthenium(II) precursor (A = $[\text{B}\{\text{C}_6\text{H}_3(\text{CF}_3)_2\}_4]$).

upon treatment of the precursors $[\text{Ru}(\kappa^1\text{-O}_2\text{CR})(\kappa^2\text{-O}_2\text{CR})(=\text{C}=\text{CHPh})(\text{P}i\text{Pr}_3)_2]$ with $[\text{H}(\text{OEt}_2)_2][\text{B}\{\text{C}_6\text{H}_3(\text{CF}_3)_2\}_4]$. Although all the products of these protonation reactions (the cationic carbyne as well as the cyclic carbene compounds) are quite stable (three of them have been characterized crystallographically), they are poor catalysts in olefin metathesis [40]. This is true also for the dicationic ruthenium carbene **45**, which has been prepared by protonation of the monocationic vinyl compound **44**, the latter being formed by insertion of the vinylidene ligand into the Ru–H bond of **25** (see Scheme 1.8-16) [41].

A highly active catalytic species (**50**), probably with the composition shown in Scheme 1.8-17, is generated upon treatment of **48** with HBF_4 in ether at -78°C [42]. The precursors for the two hydrido(vinylidene) complexes **48** and **49** are the corresponding hydrido(dihydrogen)-ruthenium(II) derivatives **46** and **47**, which were prepared similarly to the PCy_3 counterpart **20** from $\text{RuCl}_3\cdot\text{aq}$, isoprene, and $t\text{Bu}_2\text{PCH}_2\text{XC}_6\text{H}_5$ (X = CH_2 , CH_2O) in 2-propanol/THF under a hydrogen atmosphere in the presence of NEt_3 . The use of the particular phosphines was motivated by the assumption that the phenyl group in the side chain could stabilize



Scheme 1.8-17. Preparation of a catalytically active carbyne(hydrido)ruthenium(II) complex used for ROMP of cyclooctene (L = $tBu_2PCH_2XC_6H_5$ with X = CH₂ and OCH₂).

some intermediates by π -coordination of the six-membered ring to the metal and thus protect these intermediates from decomposition.

This strategy was partly fulfilled in both rhodium [43] and ruthenium chemistry [42, 44]. With regard to the catalytic activity of **50** in ROMP of cyclooctene, it was shown that the rate of formation of the corresponding polymer is significantly higher than when using the compound $[RuCl_2(=CHPh)(PCy_3)_2]$ as the catalyst. Under identical conditions (CD_2Cl_2 , 21 °C, ratio $c\text{-}C_8H_{14}$:**50** = 1250:1), the polymerization of cyclooctene with the *in situ*-generated catalyst **50** is finished after about 8 min, whereas with the Grubbs carbene, in the same period of time, only 15% of the olefin is polymerized. To rationalize this difference, we assume that the dissociation of one phosphine ligand to give the catalytically active species is faster for the carbyne cation than for the neutral carbene complex.

1.8.4

Conclusions

Following the isolation of the first ruthenium carbene by Christian and Roper in 1974 [6], a great number (probably more than 200) of other carbeneruthenium(0) and carbeneruthenium(II) complexes have been prepared. Among these compounds containing $Ru=CRR'$ as the building block, those of the Grubbs type with the general composition $[RuCl_2(=CHR)(PCy_3)_2]$, including the second generation, where one of the tricyclohexylphosphine ligands is replaced by an imidazoylidene, have become most prominent. They are not only highly efficient catalysts for olefin

metathesis but also are increasingly used in organic synthesis and even in the preparation of new polymers [45].

The secret of this unique role for the five-coordinate ruthenium carbenes certainly lies in the coordination sphere, in particular in the nature of the neutral ligands, which provide the balance between stability and lability (i.e., reactivity). Because, owing to our present knowledge, a four-coordinate ruthenium carbene with a 14-electron count is the active species, the precursor should have a 16-electron count and a 2-electron donor ligand readily dissociating under catalytic conditions. Although some of our investigations have shown that mono- as well as dicationic ruthenium(II) carbenes seem to be less suitable as catalysts in olefin metathesis, some recent reports by Hofmann and Chen [46] argue against this assumption. One promising modification of the original ruthenium carbenes could be the substitution of the carbene by a vinylidene, particularly because the rearrangement of a terminal alkyne to the isomeric vinylidene is a favored process in the coordination sphere of ruthenium(II). Both the results about the reactivity of complexes such as **25** and **26** (see Scheme 1.8-14) and recent observations by Ozawa [47] and Grubbs [48] are in favor of this prospect.

Acknowledgements

We would like to acknowledge the activity and enthusiasm of those members of our group who participated in the research on rhodium and ruthenium carbene complexes and whose names are mentioned in the list of references. Moreover, we are highly indebted to those coworkers who did the crystallographic investigations. Most of the catalytic studies were carried out in collaboration with the group of Michael Schulz and Peter Schwab at BASF, Ludwigshafen, for which we are very grateful. We also thank the Deutsche Forschungsgemeinschaft (SFB 347), the Fonds der Chemischen Industrie, and BASF AG for continuous financial support.

References

- 1 E. O. FISCHER, A. MAASBÖL, *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 580.
- 2 a) K. H. DÖTZ, H. FISCHER, P. HOFMANN, F. R. KREISSL, U. SCHUBERT, K. WEISS, *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim, **1983**. b) U. SCHUBERT (Ed.), *Advances in Metal Carbene Chemistry*, Kluwer Academic, Dordrecht, **1989**. c) F. Z. DÖRWALD, *Metal Carbenes in Organic Synthesis*, Wiley-VCH, Weinheim, **1999**.
- 3 a) E. O. FISCHER, *Pure Appl. Chem.* **1970**, 24, 407–423. b) E. O. FISCHER, *Pure Appl. Chem.* **1972**, 30, 353–372. c) E. O. FISCHER, *Angew. Chem.* **1974**, 86, 651–663. d) E. O. FISCHER, *Adv. Organomet. Chem.* **1976**, 14, 1–32.
- 4 a) R. R. SCHROCK, *J. Am. Chem. Soc.* **1974**, 96, 6796–6797. b) R. R. SCHROCK, *Acc. Chem. Res.* **1979**, 12, 98–104. c) R. R. SCHROCK, *J. Organomet. Chem.* **1986**, 300, 249–262. d) J. FELDMANN, R. R. SCHROCK, *Progr. Inorg. Chem.* **1991**, 39, 1–74.
- 5 W. A. HERRMANN, *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 800–813.
- 6 a) W. R. ROPER, *J. Organomet. Chem.* **1986**, 300, 167–190. b) M. A. GALLOP, W. R. ROPER, *Adv. Organomet. Chem.* **1986**, 25, 121–198.
- 7 Representative papers: a) F. J. GARCIA

- ALONSO, A. HÖHN, J. WOLF, H. OTTO, H. WERNER, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 406–407. b) H. WERNER, F. J. GARCIA ALONSO, H. OTTO, J. WOLF, *Z. Naturforsch. B* **1988**, *43*, 722–726. c) H. WERNER, U. BREKAU, *Z. Naturforsch. B* **1989**, *44*, 1438–1446. d) T. RAPPERT, O. NÜRNBERG, N. MAHR, J. WOLF, H. WERNER, *Organometallics* **1992**, *11*, 4156–4164. e) H. WERNER, T. RAPPERT, *Chem. Ber.* **1993**, *126*, 669–678. f) H. WERNER, T. RAPPERT, R. WIEDEMANN, J. WOLF, N. MAHR, *Organometallics* **1994**, *13*, 2721–2727.
- 8 Summarizing articles: a) H. WERNER, *Nachr. Chem. Tech. Lab.* **1992**, *40*, 435–444. b) H. WERNER, *J. Organomet. Chem.* **1994**, *475*, 45–55. c) H. WERNER, *Chem. Commun.* **1997**, 903–910.
- 9 Leading references: a) M. SCHÄFER, N. MAHR, J. WOLF, H. WERNER, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1315–1318. b) H. WERNER, M. SCHÄFER, J. WOLF, K. PETERS, H. G. VON SCHNERING, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 191–194. c) H. WERNER, R. WIEDEMANN, P. STEINERT, J. WOLF, *Chem. Eur. J.* **1997**, *3*, 127–137. d) M. LAUBENDER, H. WERNER, *Chem. Eur. J.* **1999**, *5*, 2937–2946. e) H. WERNER, R. WIEDEMANN, M. LAUBENDER, B. WINDMÜLLER, J. WOLF, *Chem. Eur. J.* **2001**, *7*, 1959–1967. f) H. WERNER, R. WIEDEMANN, M. LAUBENDER, B. WINDMÜLLER, P. STEINERT, O. GEVERT, J. WOLF, *J. Am. Chem. Soc.* **2002**, *124*, 6966–6980.
- 10 J. WOLF, L. BRANDT, A. FRIES, H. WERNER, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 510–512.
- 11 a) P. SCHWAB, N. MAHR, J. WOLF, H. WERNER, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1480–1482. b) H. WERNER, P. SCHWAB, E. BLEUEL, N. MAHR, P. STEINERT, J. WOLF, *Chem. Eur. J.* **1997**, *3*, 1375–1384.
- 12 H. WERNER, P. SCHWAB, E. BLEUEL, N. MAHR, B. WINDMÜLLER, J. WOLF, *Chem. Eur. J.* **2000**, *6*, 4461–4470.
- 13 N. MAHR, Dissertation, Universität Würzburg, **1994**.
- 14 M. GANDELMAN, B. RYBTCHINSKI, N. ASHKENAZI, R. GAUVIN, D. MILSTEIN, *J. Am. Chem. Soc.* **2001**, *123*, 5372–5373.
- 15 E. BLEUEL, B. WEBERNDÖRFER, H. WERNER, *J. Organomet. Chem.* **2001**, *617*–618, 502–510.
- 16 A. PADWA, D. J. AUSTIN, A. T. PRICE, M. A. SEMONES, M. P. DOYLE, M. N. PROTOPOPOVA, W. R. WINCHESTER, A. TRAN, *J. Am. Chem. Soc.* **1993**, *115*, 8669–8680.
- 17 H. WERNER, M. E. SCHNEIDER, M. BOSCH, J. WOLF, J. H. TEUBEN, A. MEETSMA, S. I. TROYANOV, *Chem. Eur. J.* **2000**, *6*, 3052–3059.
- 18 a) P. SCHWAB, M. B. FRANCE, J. W. ZILLER, R. H. GRUBBS, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041. b) P. SCHWAB, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- 19 a) H. WERNER, A. STARK, M. SCHULZ, J. WOLF, *Organometallics* **1992**, *11*, 1126–1130. b) H. WERNER, A. STARK, P. STEINERT, C. GRÜNWALD, J. WOLF, *Chem. Ber.* **1995**, *128*, 49–62. c) M. MARTIN, O. GEVERT, H. WERNER, *J. Chem. Soc., Dalton Trans.* **1996**, 2275–2283.
- 20 a) C. GRÜNWALD, O. GEVERT, J. WOLF, P. GONZÁLEZ-HERRERO, H. WERNER, *Organometallics* **1996**, *15*, 1960–1962. b) J. WOLF, W. STÜER, C. GRÜNWALD, O. GEVERT, M. LAUBENDER, H. WERNER, *Eur. J. Inorg. Chem.* **1998**, 1827–1834.
- 21 a) M. L. CHRIST, S. SABO-ETIENNE, B. CHAUDRET, *Organometallics* **1994**, *13*, 3800–3804. b) T. BURROW, S. SABO-ETIENNE, B. CHAUDRET, *Inorg. Chem.* **1995**, *34*, 2470–2472.
- 22 S. T. NGUYEN, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.
- 23 a) J. P. SELEGUE, *Organometallics* **1982**, *1*, 217–218. b) H. LE BOZEC, K. OUZZINE, P. H. DIXNEUF, *J. Chem. Soc., Chem. Commun.* **1989**, 219–221. c) D. PILETTE, K. OUZZINE, H. LE BOZEC, P. H. DIXNEUF, C. E. F. RICKARD, W. R. ROPER, *Organometallics* **1992**, *11*, 809–817.
- 24 M. OLIVAN, O. EISENSTEIN, K. G. CAULTON, *Organometallics* **1997**, *16*, 2227–2229.

- 25 T. E. WILHELM, R. T. BELDERRAIN, S. N. BROWN, R. H. GRUBBS, *Organometallics* **1997**, *16*, 3867–3869.
- 26 H. KATAYAMA, F. OZAWA, *Organometallics* **1998**, *17*, 5190–5196.
- 27 R. T. BELDERRAIN, R. H. GRUBBS, *Organometallics* **1997**, *16*, 4001–4003.
- 28 J. WOLF, W. STÜER, C. GRÜNWALD, H. WERNER, P. SCHWAB, M. SCHULZ, *Angew. Chem. Int. Ed.* **1998**, *37*, 1124–1126.
- 29 W. STÜER, Dissertation, Universität Würzburg, **1999**.
- 30 W. STÜER, personal communication.
- 31 a) L. PORRI, R. ROSSI, P. DEVERSI, G. ALLEGRA, *Tetrahedron Lett.* **1965**, 4187–4189. b) Improved procedure: D. N. COX, R. ROULET, *Inorg. Chem.* **1990**, *29*, 1360–1365.
- 32 a) L. PORRI, R. ROSSI, P. DEVERSI, A. LUCCHERINI, *Makromol. Chem.* **1974**, *175*, 3097–3115. b) L. PORRI, P. DEVERSI, A. LUCCHERINI, R. ROSSI, *Makromol. Chem.* **1975**, *176*, 3121–3125. c) W. A. HERRMANN, W. C. SCHATTENMANN, O. NUYKEN, S. C. GLANDER, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1087–1088.
- 33 H. WERNER, W. STÜER, S. JUNG, B. WEBERNDÖRFER, J. WOLF, *Eur. J. Inorg. Chem.* **2002**, 1076–1080.
- 34 W. STÜER, J. WOLF, H. WERNER, *J. Organomet. Chem.* **2002**, *641*, 203–207.
- 35 a) M. S. SANFORD, J. A. LOVE, R. H. GRUBBS, *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554. b) L. CAVALLO, *J. Am. Chem. Soc.* **2002**, *124*, 8965–8973.
- 36 W. STÜER, J. WOLF, H. WERNER, P. SCHWAB, M. SCHULZ, *Angew. Chem. Int. Ed.* **1998**, *37*, 3421–3423.
- 37 J. ESPUELAS, M. A. ESTERUELAS, F. J. LAHOZ, L. A. ORO, N. RUIZ, *J. Am. Chem. Soc.* **1993**, *115*, 4683–4689.
- 38 A. SCHÄFER, unpublished results; cited in ref. [36].
- 39 a) P. GONZÁLEZ-HERRERO, B. WEBERNDÖRFER, K. ILG, J. WOLF, H. WERNER, *Angew. Chem. Int. Ed.* **2000**, *39*, 3266–3269. b) P. GONZÁLEZ-HERRERO, B. WEBERNDÖRFER, K. ILG, J. WOLF, H. WERNER, *Organometallics* **2001**, *20*, 3672–3685.
- 40 P. GONZÁLEZ-HERRERO, unpublished results.
- 41 S. JUNG, K. ILG, J. WOLF, H. WERNER, *Organometallics* **2001**, *20*, 2121–2123.
- 42 S. JUNG, K. ILG, C. D. BRANDT, J. WOLF, H. WERNER, *J. Chem. Soc., Dalton Trans.* **2002**, 318–327.
- 43 a) H. WERNER, G. CANEPA, K. ILG, J. WOLF, *Organometallics* **2000**, *19*, 4756–4766. b) G. CANEPA, Dissertation, Universität Würzburg, **2002**.
- 44 S. JUNG, Dissertation, Universität Würzburg, **2001**.
- 45 a) K. J. IVIN, J. C. MOL, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, USA, **1997**. b) M. SCHUSTER, S. BLECHERT, *Angew. Chem. Int. Ed.* **1997**, *36*, 2036–2055. c) A. FÜRSTNER, *Top. Catal.* **1997**, *4*, 285–299. d) R. H. GRUBBS, S. CHANG, *Tetrahedron* **1998**, *54*, 4413–4450. e) A. FÜRSTNER, *Synlett* **1999**, 1523–1533. f) M. E. MAIER, *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077. g) A. FÜRSTNER, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043. h) T. M. TRNKA, R. H. GRUBBS, *Acc. Chem. Res.* **2001**, *34*, 18–29.
- 46 a) S. M. HANSEN, F. ROMINGER, M. METZ, P. HOFMANN, *Chem. Eur. J.* **1999**, *5*, 557–566. b) M. A. U. VOLLAND, C. ADLHART, C. A. KIENER, P. CHEN, P. HOFMANN, *Chem. Eur. J.* **2001**, *7*, 4621–4632.
- 47 H. KATAYAMA, H. URUSHIMA, F. OZAWA, *J. Organomet. Chem.* **2000**, *606*, 16–25.
- 48 R. H. GRUBBS, personal communication.

1.9

Mechanism of Ruthenium-Catalyzed Olefin Metathesis Reactions

Melanie S. Sanford and Jennifer A. Love

1.9.1

Introduction

Mechanistic studies have played an integral role in the evolution of ruthenium-based olefin metathesis catalysts. Detailed mechanistic investigation of each generation of ruthenium catalysts has guided the development of new ligand systems that provide increased activity, improved functional group tolerance, and higher thermal stability. This chapter will review our constantly evolving mechanistic understanding of ruthenium-catalyzed olefin metathesis reactions. The mechanism of catalyst initiation, turnover, and decomposition in the widely used “first-” and “second-generation” ruthenium catalysts **1** and **2** (Figure 1.9-1) will be described, and the effects of ligand substitution on each of these parameters will be explored. Finally, the implications of mechanistic studies for the application of catalysts currently in use and for the design of new olefin metathesis catalyst systems will be discussed.

1.9.2

First-Generation Bis-Phosphine Catalyst Systems

1.9.2.1

General Mechanistic Considerations

The first comprehensive mechanistic investigation of ruthenium benzylidene **1** focused on the catalytic ring-closing metathesis (RCM) of diethyl diallylmalonate (Scheme 1.9-1) [1]. Notably, this transformation has subsequently been used as a benchmark for the comparison of dozens of first-generation ruthenium metathesis catalysts. In these systems, ring closing typically proceeds cleanly and quantitatively, and on a time scale that can be conveniently monitored by ^1H NMR spectroscopy (k_{obs} [RCM]) $\sim 10^{-3}$ – 10^{-4} at 30 °C).

These early studies provided three critical mechanistic insights into olefin metathesis reactions catalyzed by **1** [1]. First, the rate of product formation was dra-

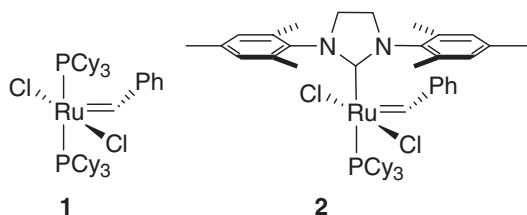
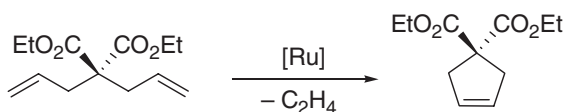
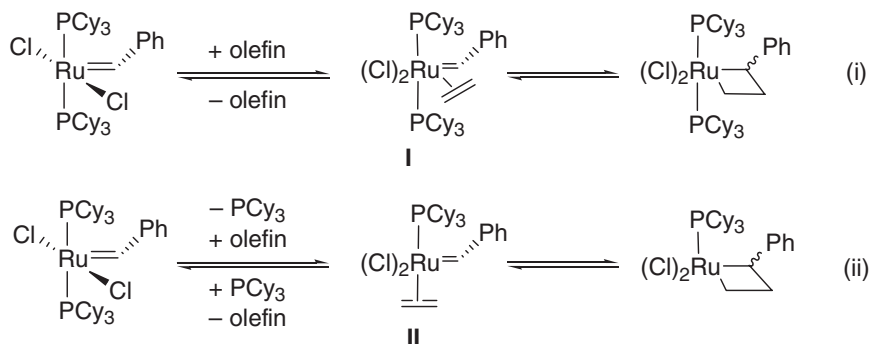


Fig. 1.9-1. Olefin metathesis catalysts **1** and **2**.



Scheme 1.9-1. RCM of DDM.

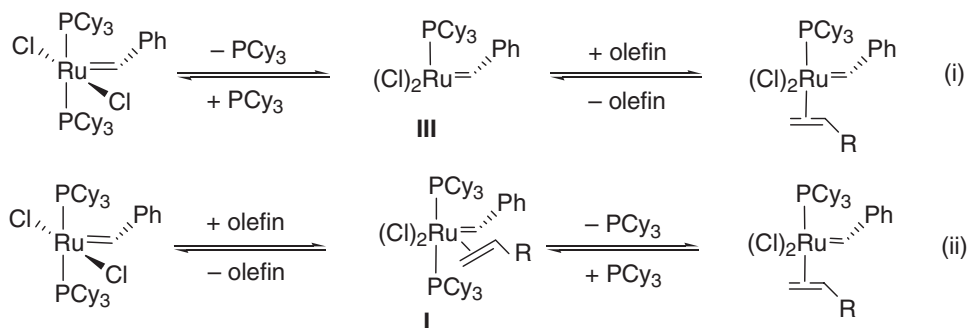


Scheme 1.9-2. Associative versus dissociative olefin metathesis mechanism.

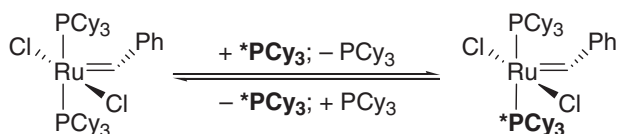
matically depressed by the addition of free PCy_3 , suggesting that phosphine dissociation is necessary for catalyst turnover. Second, a plot of k_{obs} (RCM) versus $1/[\text{PCy}_3]$ was linear with an intercept very close to zero (intercept = 2.4×10^{-4}), indicating that this “dissociative” pathway accounts for greater than 95% of catalytic activity. Finally, the ring-closing reaction proceeded with first-order kinetics in both catalyst and diene, in agreement with a simple bimolecular interaction between the diene substrate and the ruthenium center.

These results effectively rule out an “associative” olefin metathesis reaction mechanism involving metallacycle formation from the 18-electron bis-phosphine/olefin intermediate (**I**) (Scheme 1.9-2, i). Instead, these data provide strong support for an overall “dissociative” reaction mechanism (Scheme 1.9-2, ii), in which the metallacyclobutane is generated from a 16-electron monophosphine/olefin intermediate **II**. Most importantly, the proposed mechanism requires that catalyst initiation involve substitution of one PCy_3 ligand of **1** with an equivalent of the olefinic substrate.

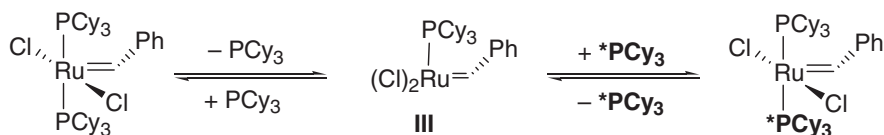
In order to gain an improved understanding of the critical catalyst initiation step, the mechanism of ligand substitution reactions at **1** was investigated in detail.



Scheme 1.9-3. Dissociative versus associative ligand exchange mechanisms.



Scheme 1.9-4. Degenerate exchange of free and bound phosphine.

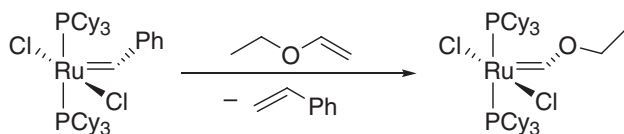


Scheme 1.9-5. Dissociative mechanism for phosphine exchange.

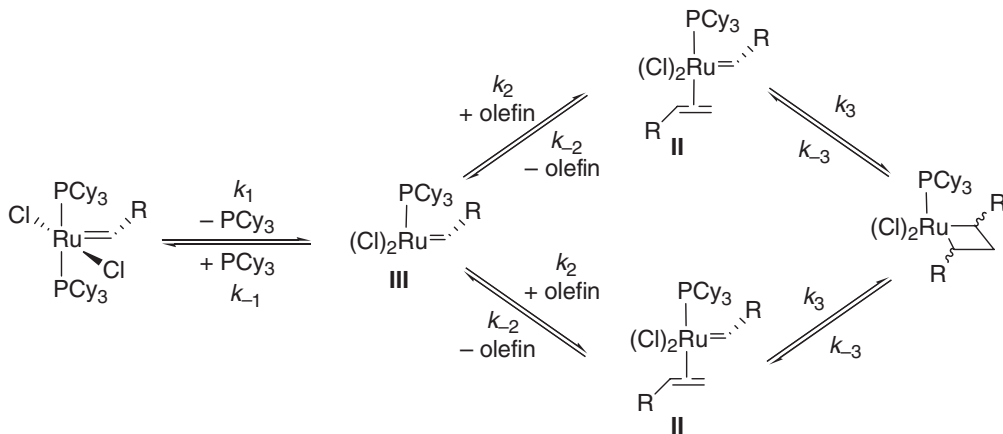
In the two limiting extremes, substitution could proceed by a dissociative pathway (involving the 14-electron intermediate $(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$, **III**) or by an associative pathway (involving the 18-electron intermediate $(\text{PCy}_3)_2(\text{Cl})_2(\text{olefin})\text{Ru}=\text{CHPh}$, **I**) (Scheme 1.9-3, **i** and **ii**, respectively).

Initial studies focused on the simplest ligand substitution reaction possible in this system – the degenerate exchange of free and bound PCy_3 (Scheme 1.9-4) [2]. Using ^{31}P NMR magnetization transfer experiments, the rate of phosphine exchange was monitored as a function of phosphine concentration and temperature. These investigations revealed that the pseudo first-order rate constant for exchange (k_1) is independent of $[\text{PCy}_3]$, indicating that the rate expression does not contain a phosphine term. Additionally, the activation entropy for phosphine substitution is large and positive in sign ($\Delta S^\ddagger \sim 12$ eu), suggesting increased disorder in the transition state. Both of these results implicate the dissociative phosphine exchange (Scheme 1.9-5).

Next, the mechanism of phosphine/olefin substitution (i.e., catalyst initiation) was directly examined by monitoring the reaction of **1** with ethyl vinyl ether [2]. This electron-rich olefinic substrate was selected because it is known to react rapidly, quantitatively, regioselectively, and irreversibly with catalyst **1** to produce a Fischer carbene complex and styrene (Scheme 1.9-6) [3, 4]. As such, this substrate



Scheme 1.9-6. Reaction with ethyl vinyl ether.



Scheme 1.9-7. Overall mechanism.

serves to trap all metathesis-active ruthenium species after a single catalyst turnover, providing a direct, stoichiometric probe for catalyst initiation.

The reaction of **1** with ethyl vinyl ether was monitored by ^1H NMR and UV-vis spectroscopy as a function of [olefin] [2]. This reaction exhibits classic saturation kinetics, with a rate constant (k_{obs}) that becomes independent of [ethyl vinyl ether] at high olefin concentrations (>2.5 M). Importantly, the value of k_{obs} at saturation is identical to the rate constant for phosphine exchange (k_1), demonstrating that phosphine dissociation becomes rate determining under these conditions. These experiments confirm that both phosphine/phosphine and phosphine/olefin substitutions at **1** proceed by a dissociative reaction mechanism (Scheme 1.9-3, i).

An overall catalytic cycle for ruthenium catalyst **1** that is consistent with all currently available mechanistic data is outlined in Scheme 1.9-7 [2]. The first step, catalyst initiation, involves dissociation of one PCy_3 ligand to afford the highly reactive monophosphine intermediate **III**. Although this intermediate has not been observed directly by NMR spectroscopy in solution (indicating that $k_{-1}/k_1 > 10^2$), **III** has been identified in the gas phase using mass spectrometric techniques [5]. In a second step, the reaction of **III** with an olefinic substrate generates the monophosphine/olefin complex **II**. Notably, with appropriate choice of olefinic substrate, catalytically viable monophosphine/olefin intermediates such as **II** can be isolated and structurally characterized [6]. Finally, in a third step, coupling of the olefin and alkylidene ligands within the coordination sphere of the ruthenium produces metallacyclobutane **IV**. This metallacycle can break down productively to form a new olefin and a new alkylidene product or unproductively to regenerate

the starting materials. Importantly, ruthenacyclobutanes have never been detected in olefin metathesis reactions catalyzed by **1**, and it is possible that **IV** serves as a transition state rather than a discrete intermediate along this reaction coordinate [5].

According to the mechanism outlined in Scheme 1.9-7, the overall catalytic activity of **1** is dictated by the relative rates of three processes: (1) phosphine dissociation (initiation) (k_1), (2) phosphine re-coordination (k_{-1}), and (3) olefin binding (k_2)*. High catalytic activity is anticipated when catalyst initiation is efficient (i.e., k_1 is large) and when the resulting 14-electron intermediate **III** reacts rapidly with olefinic substrates relative to free phosphine (i.e., k_{-1}/k_2 is small). These conditions serve to maximize the availability of **III**, and thereby allow many olefin metathesis turnovers to take place before phosphine re-coordination.

The critical values of k_{-1} and k_2 have not been measured directly for catalyst **1**, because the intermediates involved cannot be detected in solution. However, the k_{-1}/k_2 ratio for the reaction of **1** with ethyl vinyl ether has been determined experimentally from a plot of the inverse of the initiation rate constant ($1/k_{\text{obs}}$) versus $[\text{PR}_3]/[\text{ethyl vinyl ether}]$ [2]. The large magnitude of this ratio [k_{-1}/k_2 (ethyl vinyl ether) = 1.3×10^4] indicates that the coordinatively unsaturated intermediate $(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$ (**III**) has a high affinity for binding free PCy_3 , even in the presence of a large excess of highly coordinating, electron-rich olefinic substrates such as ethyl vinyl ether. This value is consistent with the extremely low reactivity of **1** towards electron-poor olefinic substrates such as acrylates and perfluoroalkyl-substituted alkenes [7].

1.9.2.2

Substituent Effects in Ruthenium-Catalyzed Olefin Metathesis

The mechanism of olefin metathesis reactions catalyzed by a series of bis-phosphine complexes of the general formula $(\text{PR}_3)_2(\text{X})_2\text{Ru}=\text{CHR}^1$ has been examined in detail [1, 8]. In general, these investigations indicate that perturbation of the ancillary ligands does not change the overall dissociative mechanism of ruthenium-catalyzed olefin metathesis reactions (Scheme 1.9-7). However, variation of PR_3 , X , and CHR^1 does have a significant impact on both the initiation rates and the overall catalytic activity of these catalysts. Some of the observed trends in catalyst initiation and activity as a function of ancillary ligand substitution are described in detail below.

The catalytic activity of the ruthenium alkylidenes $(\text{PR}_3)_2(\text{X})_2\text{Ru}=\text{CHPh}$ in the RCM of diethyl diallylmalonate varies by more than an order of magnitude upon substitution of the phosphine (PR_3) and the X-type ligands [1]. For example, replacing the chloride ligands of **1** with larger and more electron-donating bromides or iodides leads to an almost 20-fold decrease in catalyst turnover rates (k_{obs} (RCM) for $\text{Cl} > \text{Br} \gg \text{I}$). Similarly, substitution of PCy_3 with smaller and less electron-

*) This assumes that the rate of oxidative addition to produce the metallacyclobutane intermediate is fast. If metallacycle formation

is slow, then the magnitude of k_3 will also contribute significantly to overall catalytic activity.

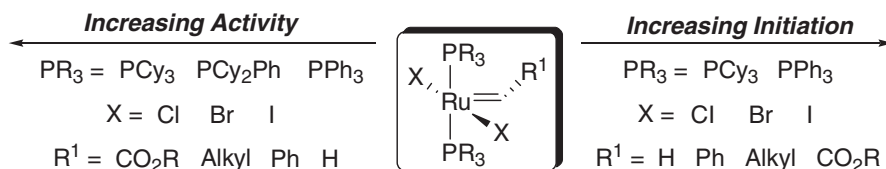


Fig. 1.9-2. Comparison of activity and initiation.

donating phosphine ligands results in up to a 10-fold decrease in RCM activity (k_{obs} (RCM) for $\text{PCy}_3 > \text{PCy}_2\text{Ph} > \text{PCyPh}_2$). Furthermore, the bis- PPh_3 complex $(\text{PPh}_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}$ is essentially unreactive towards the diene substrate.

These trends in metathesis activity as a function of X and PR_3 substitution can be explained based on the ability of the ancillary ligands to promote [2+2] cycloaddition (a formal oxidative addition reaction) and to stabilize the resulting Ru(IV) metallacyclobutane. In general, electron-donating phosphine ligands (e.g., PCy_3) promote oxidative addition reactions at M^n by stabilizing the electron-deficient M^{n+2} product [9]. Similarly, small and highly electronegative chloride ligands are well known to stabilize high oxidation state metal centers, particularly relative to softer and more polarizable bromides and iodides [9]. Importantly, however, the steric and electronic requirements of other olefin metathesis intermediates (e.g., olefin adduct **II** and/or 14-electron monophosphine species **III**) also may contribute significantly to the ancillary ligand effects observed in this system.

The rate of catalyst initiation also varies dramatically upon ancillary ligand substitution [8]. Surprisingly, however, the observed trends in initiation in these catalyst systems are generally opposite to those in overall activity – in other words, catalysts exhibiting higher overall activity often exhibit lower initiation rates. In one example, the substitution of PCy_3 in $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHR}'$ with smaller and less electron-donating PPh_3 ligands results in a 10-fold increase in k_1 [10]. Similarly, changing the chloride ligands of $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}$ to larger and less electronegative iodides results in an approximately 10^2 enhancement in catalyst initiation (k_1 for $\text{I} \gg \text{Br} > \text{Cl}$) [8]. The kinetics of catalyst initiation are also dramatically influenced by the nature of the alkylidene moiety, and k_1 increases by about four orders of magnitude as R' is varied from H to CO_2R (k_1 for $\text{H} \ll \text{Ph} < \text{alkyl} < \text{CO}_2\text{R}$) (Figure 1.9-2) [8, 11].

The substituent effects on initiation can be rationalized based on the fact that this reaction proceeds via PR_3 dissociation from the starting complex $(\text{PR}_3)_2(\text{X})_2\text{Ru}=\text{CHR}^1$. Lowering the basicity of the phosphine ligand from PCy_3 [$\text{pK}_a = 9.7$] to PPh_3 [$\text{pK}_a = 2.7$] is expected to promote PR_3 dissociation by decreasing the strength of the Ru–P interaction. Similarly, increasing the size of the halide ligands from Cl to I should lower the barrier to PR_3 loss due to the increased steric congestion at the ruthenium center. The effects of alkylidene substitution on initiation are less well understood, but both steric and electronic factors likely contribute to the high initiation rates of ester-substituted carbenes relative to methylidenes. Importantly, the origin of all of these ancillary ligand effects remains the topic of considerable theoretical and experimental investigation.

1.9.2.3

Thermal Decomposition of Ruthenium Catalysts

The mechanism of catalyst decomposition has been the subject of substantial research effort because it has important implications for the application of ruthenium-based olefin metathesis catalysts in both polymer chemistry and total synthesis [12]. The thermal decomposition of **1** plays a critical role in limiting catalyst turnover numbers, particularly in metathesis reactions of challenging substrates (highly substituted or electron-poor olefins) that require forcing conditions (elevated temperatures, extended reaction times) or high dilution to reach completion. Furthermore, ruthenium decomposition products can contribute to undesirable side reactions such as olefin isomerization.

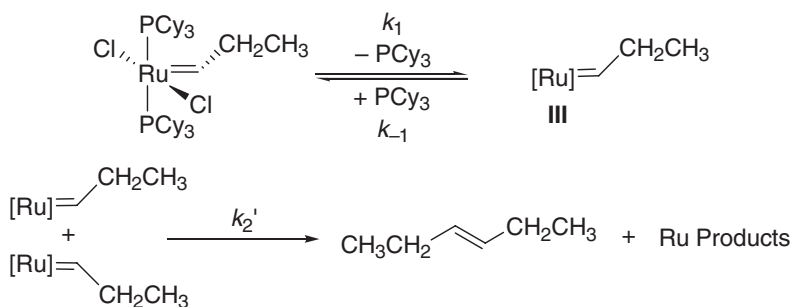
The thermal decomposition of two first-generation ruthenium olefin metathesis catalysts – the propylidene $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHCH}_2\text{CH}_3$ (**3**) and the methylidene $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CH}_2$ (**4**) – has been investigated in detail [12]. These complexes were selected because both ruthenium alkylidenes (as modeled by propylidene **3**) and ruthenium methylidene **4** serve as critical intermediates in ROMP, RCM, CM, and ADMET reactions initiated by **1**. Additionally, the thermal decomposition of **3** and **4** occurs on a time scale that is conveniently monitored by ^1H NMR spectroscopy.

Propylidene decomposition proceeds relatively slowly at 55°C ($t_{1/2} = 8$ h, $[\text{Ru}] = 0.023$ M), highlighting the excellent thermal stability of this catalyst [12]. (Notably, the parent benzylidene is even more stable, and under identical conditions $t_{1/2}$ for **1** is 8 days!) The major organic products of propylidene decomposition are *trans*-3-hexene (derived from dimerization of the alkylidene fragment) and free PCy_3 , while the inorganic products consist of a mixture of unidentified ruthenium species including several metal hydrides. Notably, as the reaction progresses, Ru-hydride-catalyzed isomerization of *trans*-3-hexene produces a mixture of hexene products.

The kinetics data for propylidene decomposition do not fit simple first- or second-order rate expressions, presumably due to secondary reactions and/or interference of the multiple decomposition products with the primary decomposition event [12]. Although the data show a reasonably linear second-order fit at intermediate times, significant deviations from linearity are observed at the beginning of the reaction. Nevertheless, the rate of propylidene decomposition is clearly inhibited by the addition of free PCy_3 , suggesting that phosphine dissociation is required for this transformation.

Both product and kinetic analysis of propylidene thermolysis point to the decomposition mechanism that is outlined in Scheme 1.9-8. In a first step, phosphine dissociation from catalyst **3** produces the 14-electron intermediate **III**. This coordinatively unsaturated ruthenium fragment then undergoes bimolecular coupling to generate 3-hexene and a mixture of inorganic products. Significantly, this mechanism suggests that there should be a direct correlation between the rates of catalyst initiation and catalyst decomposition in ruthenium alkylidenes.

The thermal decomposition of ruthenium methylidene **4** proceeds in a com-



Scheme 1.9-8. Mechanism of propylidene decomposition.

pletely different fashion from that of the closely related propylidene **3** [12]. First, the methylidene exhibits significantly lower thermal stability, and $t_{1/2}$ for **4** is only 40 min at 55 °C. Second, the products of methylidene thermolysis include free PCy₃ and a mixture of ruthenium species, but ethylene (the expected product of methylidene dimerization) is not observed in the reaction mixture. Instead, deuterium labeling studies reveal that deuterium from the methylidene fragment is incorporated into the phosphine ligands of the decomposition products. Even more surprisingly, the kinetics data indicate that methylidene decomposition is a clean first-order reaction and is not retarded by the addition of free PCy₃. These results clearly demonstrate that methylidene decomposition is a unimolecular process and suggest that it involves intramolecular activation of a phosphine ligand.

These decomposition studies have several important implications for olefin metathesis reactions that involve ruthenium methylidene and/or alkylidene intermediates. Most notably, the unimolecular mechanism of methylidene decomposition indicates that dilution of olefin metathesis reactions will not increase the longevity of **4**. Instead, slow (or portion-wise) addition of Ru catalyst should be used to maintain a constant concentration of active catalyst throughout sluggish ring-closing or cross-metathesis reactions of terminal olefins.

These studies also reveal that both catalytic turnover and bimolecular decomposition of alkylidene complexes involve a common intermediate, **III**. As a result, efforts to enhance the activity of ruthenium alkylidenes by increasing the concentration of **III** in solution will result in a concomitant acceleration of second-order decomposition processes. For example, the addition of CuCl is known to increase the catalytic activity of (PCy₃)₂(X)₂Ru=CHR' by up to 20-fold [1]. However, the CuCl (which acts as a scavenger for free PCy₃ in solution and thereby increases the concentration of 14-electron intermediate **III**) also dramatically enhances catalyst decomposition in these systems. For instance, the value of $t_{1/2}$ for **1** at 55 °C drops from 8 days to 10 min upon the addition of 10 equivalents of CuCl [12].

In general, the utility of a given olefin metathesis catalyst is a function of the ratio of the rate of olefin metathesis turnover to the rate of catalyst decomposition. The discovery of new catalyst systems that increase this ratio remains highly desirable. These issues have been addressed both in the design of new first-generation olefin metathesis catalysts (Section 1.9.2.5) and in the development

and implementation of highly active and robust second-generation *N*-heterocyclic carbene-based catalyst systems (Section 1.9.3).

1.9.2.4

Decomposition in the Presence of Functional Groups

Ruthenium olefin metathesis catalysts are often described as “functional group tolerant” because they maintain high reactivity towards olefins in the presence of ketones, aldehydes, alcohols, acids, and even H₂O [13]. However, complex **1** can be deactivated by a number of functional groups, particularly those that coordinate strongly to the Ru center. For example, **1** decomposes rapidly in coordinating solvents such as CH₃CN, DMSO, and DMF to produce a complex mixture of ruthenium products. This catalyst is similarly unstable in the presence of CO and 1° amines and reacts with H₂ to produce the ruthenium hydrides (PCy₃)₂(Cl)₂Ru(H₂) and (PCy₃)₂(Cl)Ru(H₂)(H) [14, 15]. Additionally, **1** reacts slowly with methanol to produce a carbonyl hydride [16] and with acidic chlorinated solvents to generate [HPCy₃]Cl and ruthenium decomposition products.

Although **1** is indefinitely air stable in the solid state, solutions of this catalyst undergo rapid decomposition when exposed to dioxygen. ¹H NMR analysis indicates that the decomposition products include tricyclohexylphosphine oxide (presumably resulting from aerobic oxidation of dissociated PCy₃) and benzaldehyde, along with a mixture of ruthenium species [17].

These results indicate that catalyst **1** still requires significant improvements in functional group compatibility and in facile handling under ambient conditions. Once again, these issues have been addressed in the design of new first-generation olefin metathesis catalyst systems (Section 1.9.2.5) and in the development and implementation of highly active and robust second-generation *N*-heterocyclic carbene-based catalyst systems (Section 1.9.3).

1.9.2.5

Mechanistic Considerations in Other First-Generation Ruthenium Metathesis Catalysts

A variety of derivatives of benzylidene **1** containing monodentate and/or chelating N-, O-, P- and Cl-donor ligands (Figure 1.9-3) have been prepared and examined as catalysts for olefin metathesis reactions. In many cases, these complexes exhibit improved properties (e.g., increased catalytic activity, enhanced thermal stability, higher functional group tolerance) relative to the parent catalyst **1**. Although none have yet replaced **1** in terms of overall availability and utility, these new complexes have found some specialized applications. Additionally, these species have provided important mechanistic insights and exposed new reaction manifolds for ruthenium-catalyzed olefin metathesis reactions.

A first class of modified first-generation olefin metathesis catalysts (**5**) contains the chelating bis-phosphine ligand bis(*di-tert*-butylphosphanyl)methane (dtbpm) [18]. These complexes are constitutionally similar to **1**, in that they contain two

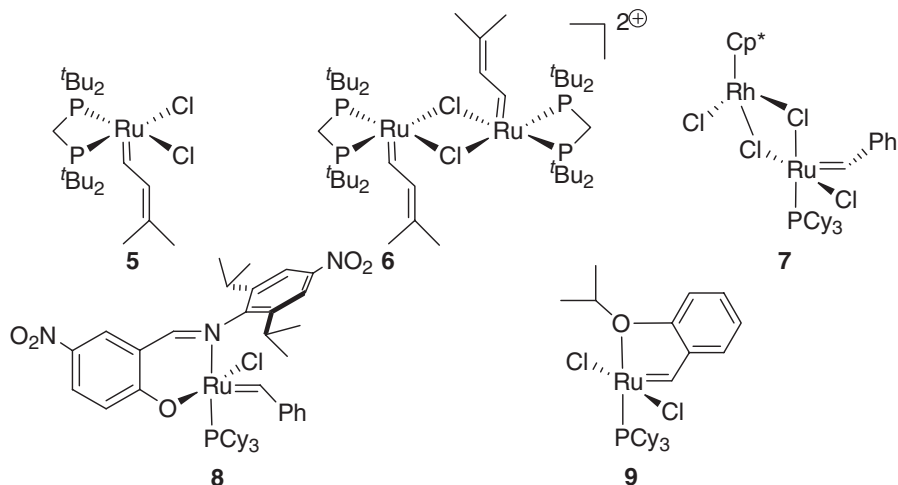
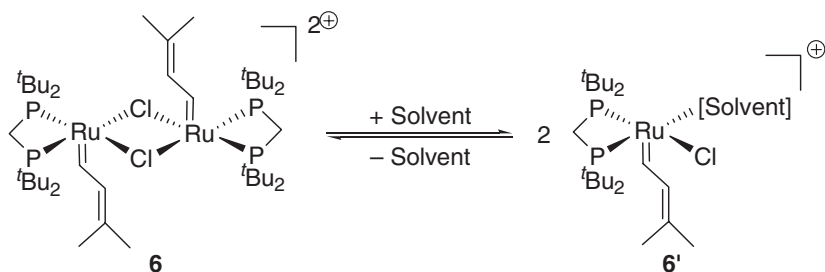


Fig. 1.9-3. Other first-generation ruthenium olefin metathesis catalysts.



Scheme 1.9-9. Equilibrium between **6** and **6'** in solution.

sterically bulky and electron-donating phosphines and two chloride ligands; however, the *cis*-orientation and chelating nature of the *dtbpm* ligand result in a dramatic reduction in olefin metathesis activity. For example, **5** is completely unreactive towards terminal olefinic substrates and exhibits low turnover frequencies in the polymerization of highly strained cyclic monomers such as norbornene (TOF = 60 h⁻¹). Only traces of a propagating alkylidene species (>10% of the total catalyst loading) are observed during norbornene polymerization, indicating that only a small portion of the ruthenium catalyst participates in the reaction. This result implicates slow initiation as the main cause for the low catalytic activity of **5**.

Further studies have shown that the olefin metathesis activity of **5** can be increased by abstraction of a chloride ligand [19]. The resulting dicationic chloride-bridged dimer **6** (in equilibrium with the monomeric complex **6'** [Scheme 1.9-9]) exhibits very high catalytic activity (more than 50 times greater than catalyst **1**) for the polymerization of cyclooctene. Both solution and gas phase [5c,d] mechanistic studies of **6** indicate that catalyst initiation involves the dissociation of a halide (or

solvento) ligand rather than a phosphine. In this system, phosphine dissociation is likely disfavored due to the sterically restricted chelate structure of the dtbpm ligand. Notably, catalyst **6** also exhibits good thermal stability, and CD_2Cl_2 solutions show no signs of decomposition after 72 h at ambient temperature under an Ar atmosphere.

Another modified first-generation catalyst system is the chloride-bridged bimetallic complex **7** (Figure 1.9-3) [20]. Catalyst **7** and its derivatives containing (*p*-cymene) RuCl_2 and (*p*-cymene) OsCl_2 bridging units are available from the reaction of **1** with half an equivalent of $[(\text{L})\text{MCl}_x]_2$. These complexes exhibit extremely high reactivity towards cyclic and acyclic olefinic substrates and carry out the ring-opening metathesis polymerization of cyclooctadiene up to 80 times faster than the parent catalyst **1**. Olefin metathesis activity increases as the bridging metal is varied from Ru to Rh, and the role of this secondary metal center is believed to involve withdrawing electron density from the bridging chlorides. The observed trend in activity (k_{obs} (ROMP) $\text{Ru} \sim \text{Os} < \text{Rh}$) is in good agreement with the increasing electronegativity of these metals.

Mechanistic analysis of polymerizations catalyzed by **7** and its derivatives has shown that the reactions exhibit no phosphine concentration dependence and are first order in [catalyst]. These results indicate that phosphine dissociation is not required for metathesis activity and are consistent with either (1) an overall associative reaction mechanism or (2) a mechanism involving full or partial dissociation of the bridging metal fragment prior to olefin coordination. Notably, the high metathesis activity of **7** and its derivatives comes at steep price – these complexes are thermally unstable and decompose almost 400 times faster than **1** at 55 °C [12]. The propensity of **7** towards thermal decomposition, along with the increased cost associated with incorporation of a second noble metal center, has limited the widespread utility of this bimetallic catalyst system.

A third series of modified first-generation olefin metathesis catalysts is exemplified by the bidentate Schiff base ruthenium adduct **8** (Figure 1.9-3) [21]. Complex **8** and its derivatives are readily available via the reaction of **1** with the thallium salts of Schiff base ligands. The most remarkable feature of these ruthenium salen adducts is their extraordinary stability towards both air/moisture and thermolysis. For example, these complexes can be purified by silica gel chromatography under ambient conditions and show no noticeable decomposition (as measured by ^1H NMR spectroscopy) after heating for hours at 80 °C.

Although **8** and its derivatives are generally less active olefin metathesis catalysts than **1** at room temperature, their reactivity increases dramatically at elevated temperatures (>60 °C) [21]. Interestingly, no propagating species is observed throughout these reactions by ^1H or ^{31}P NMR spectroscopy (indicating that <5% of the complex initiates in solution). The slow initiation of catalyst **8** may result from a requirement for imine dissociation, a process that is expected to be unfavorable due to chelate effects. The low initiation rates are likely responsible for both the high stability and relatively low reactivity of the salen catalysts. Notably, these complexes have found some important applications, particularly as a result of their unusual stability and solubility in methanol [21].

A final series of modified first-generation olefin metathesis catalysts are the aryl-ether chelates exemplified by complex **9** (Figure 1.9-3) [22]. These complexes offer the considerable advantage that they produce the same active species – $(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHR}'$ – as catalyst **1**, while exhibiting exceptionally high stability towards air and moisture. For example, like the salen complexes described above, **9** and its derivatives can be purified by column chromatography under ambient conditions. However, complex **9** initiates almost 30 times slower than the parent catalyst **1**. This slow initiation is likely due to the requirement for dissociation of the chelated ether ligand, which is expected to be unfavorable as a result of chelate effects. Catalyst **9** and its derivatives have found application as “recyclable” olefin metathesis catalysts.

1.9.3

Second-Generation Ruthenium Olefin Metathesis Catalysts

Mechanistic investigations [1, 2, 5, 8] indicate that stronger donor ligands should facilitate phosphine dissociation and thereby increase the rate of catalysis. This concept led to the use of *N*-heterocyclic carbenes (NHC) [23], which are neutral ligands with greater basicity than phosphines. Small NHC ligands generate bis(NHC) complexes of the type $(\text{NHC})_2(\text{Cl})_2\text{Ru}=\text{CHPh}$ (Figure 1.9-4) [24]. These complexes initially were reported to be more active for ROMP than **1**, and this high reactivity was attributed to the stronger donor ability of the NHC relative to PCy_3 . In fact, the NHC–Ru bond strengths were calculated to be 20–40 kcal/mol stronger than PR_3 –Ru bond strengths. However, these bis(NHC) complexes have limited utility because one NHC ligand must dissociate during the course of the reaction [24b].

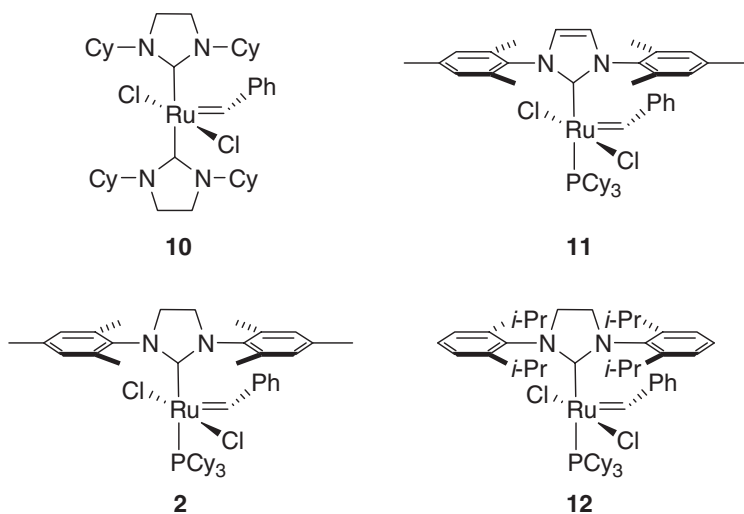


Fig. 1.9-4. Second-generation ruthenium olefin metathesis catalysts.

Several groups reported the development of bulky NHC ligands such as 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), which allowed formation of mono(NHC) complexes of the type (NHC)(PCy₃)(Cl)₂Ru=CHPh [25–27]. The resulting mixed phosphine/NHC complexes proved to be dramatically superior to the bis(NHC) and bis(phosphine) complexes in overall metathesis activity. Grubbs subsequently demonstrated that the use of an even more electron-donating ligand, 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (H₂IMes), further improved catalytic ability [28]. Importantly, these second-generation catalysts can effect metathesis of highly substituted olefins [25–30] and electron-poor olefins [7, 31]. In a number of cases, these new catalysts achieve the high activity of the Mo systems [32], while maintaining the stability and functional group compatibility that is typical of the late metal catalysts.

1.9.3.1

General Mechanistic Considerations

The improved catalytic properties of these second-generation catalyst systems were initially attributed to increased phosphine exchange rates. However, investigation of degenerate phosphine exchange and initiation kinetics for complex **2** established that phosphine dissociation from **2** is two orders of magnitude slower than from **1**. The data, along with stoichiometric initiation experiments, suggest that **2** follows a mechanistic pathway similar to that of **1**. Clearly, improved phosphine dissociation does not account for the higher catalytic activity of **2** relative to **1**. As summarized in Figure 1.9-5, the k_{-1}/k_2 ratio of **2** was determined to be 4 orders of magnitude lower than that of **1**. This increased preference for coordination of olefinic substrates relative to phosphine is likely due to the increased donor strength of the H₂IMes ligand in comparison to PCy₃. Thus, despite slow initiation, **2** remains in the catalytic cycle longer, which leads to overall faster rates of catalysis. In addition,

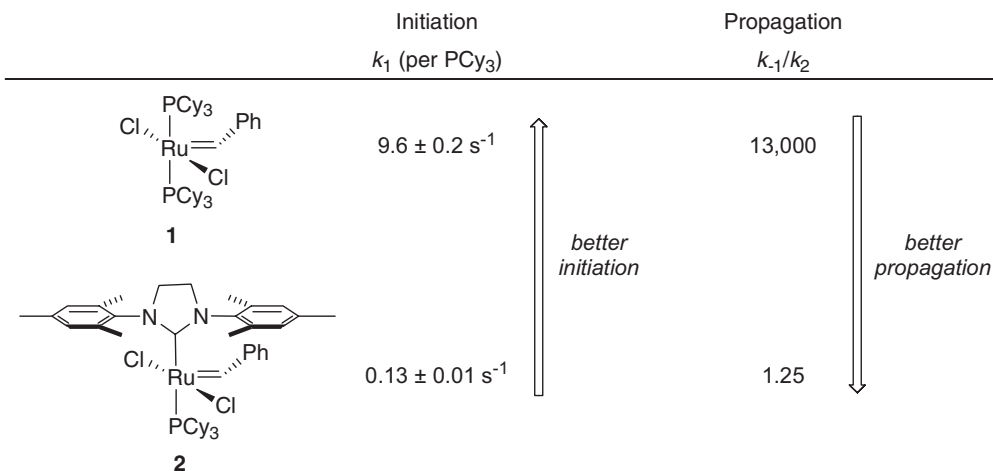


Fig. 1.9-5. Comparison of first- and second-generation catalysts.

the strong donor ability of H_2IMes relative to phosphine allows catalyst **2** to effect metathesis of olefins for which **1** is ineffective, such as electron-poor and sterically demanding olefins. It is also noteworthy that the dramatically reduced phosphine dissociation rate of **2** does not correspond to a shorter Ru–P bond in the solid state [32].

As with the bis(phosphine) catalyst **1**, the initiation rate of **2** increases with solvent polarity. This could be due to stabilization of the 14e⁻ intermediate or to associative displacement of PCy_3 with a coordinating solvent molecule. However, the use of coordinating solvents such as THF also slows catalyst propagation rates. Thus, the overall effect on reaction rate reflects both enhanced initiation and reduced propagation rates [8].

1.9.3.2

Substituent Effects in Ruthenium-Catalyzed Olefin Metathesis

Although all of the ancillary ligands influence the catalytic cycle, the dissociative mechanism is still followed irrespective of the ligand changes [8]. Similar trends were observed upon changing the X-type ligands of the second-generation catalysts, as seen with the first-generation catalysts (Figure 1.9-6). Initiation is dramatically improved by changing from Cl to Br to I, but this is offset by a comparable increase in k_{-1}/k_2 . Consequently, $(\text{H}_2\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$ and $(\text{H}_2\text{IMes})(\text{PCy}_3)(\text{I})_2\text{Ru}=\text{CHPh}$ effect ROMP of COD at a nearly comparable rate.

Changes to the alkylidene ligand also result in trends similar to those observed for the bis(phosphine) catalysts. These effects are poorly understood but are thought to involve both steric and electronic factors. Importantly, although changing the alkylidene affects initiation, catalysts differing only by their alkylidene converge to a common intermediate after a single turnover. Thus, a readily synthesized catalyst that differs from **2** only in its alkylidene can have comparable catalytic activity, as long as initiation is not significantly reduced. The methyldiene complexes $(\text{H}_2\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CH}_2$ and $(\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CH}_2$ are very poor initiators and decompose on the same time scale that they initiate. In both cases, the resultant 14e⁻ complexes are the propagating species of many RCM and CM processes; if the 14e⁻ complexes are trapped by phosphine (generating $(\text{H}_2\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CH}_2$ and $(\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CH}_2$), reentry into the catalytic cycle will be slow. Consequently, judicious choice of substrate (i.e., one without terminal olefins) can be critical to the success of a reaction.

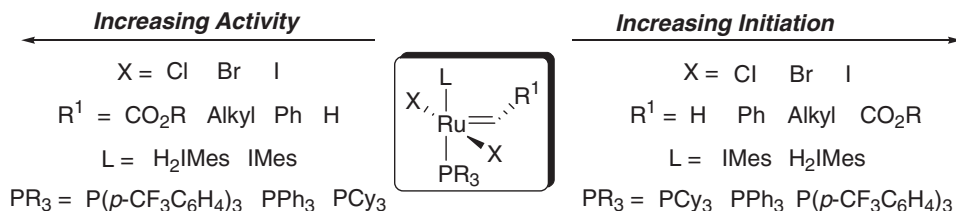
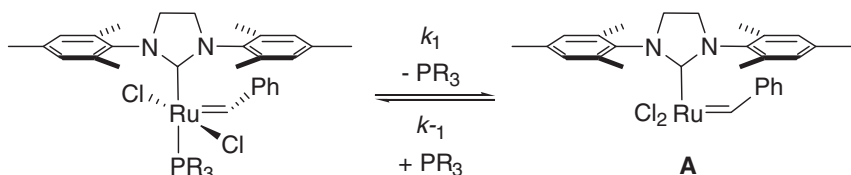


Fig. 1.9-6. Catalyst trends.



Scheme 1.9-10. Phosphine dissociation leading to common intermediate **A**.

Changes in the NHC ligand can also have a significant impact on the reaction. IMes and H₂IMes are relatively comparable, although the H₂IMes catalyst exhibits higher catalytic activity in certain cases [33]. Fürstner has recently reported a series of catalysts bearing related NHC ligands and has compared the reaction yields in several metathesis processes using these catalysts [34]. Related complex **12** has shown increased rates of product formation relative to **2**; the reasons for this improvement are not well understood but are thought to be related to improved initiation [35]. However, without detailed information about the rates of the individual reactions, it is difficult to make comparisons between catalysts. In addition, it is difficult to predict which catalyst would provide the highest yields and turnover numbers for a given substrate and reaction without a complete analysis of the individual steps. The results of this study demonstrate that subtle variation of the NHC ligand can have profound effects on the rate of catalysis. The nature of metal-carbene bonding is currently under investigation, and this information should help to elucidate the factors responsible for the increased basicity of the NHC ligands relative to phosphines.

NHC-based complexes differing only by their phosphine all provide the same propagating species upon initiation (intermediate **A**, Scheme 1.9-10). Consequently, changing the phosphine affects the rates of phosphine dissociation and rebinding, but not the reaction with olefin. Thus, unless phosphine rebinding is also significantly altered, improved initiation should increase the steady-state concentration of the active complex, leading to faster catalysis. Both steric and electronic perturbations affect phosphine dissociation, although in general, a weak donor ligand, regardless of steric size, dissociates faster than a stronger electron donor [8, 32].

The analysis of phosphine electronics is not straightforward because many factors contribute to phosphine donor strength [36]. Although using any one parameter to represent the electronics of a phosphine is an oversimplification, pK_a is typically used as a measure of the sigma-donor ability of phosphines coordinated to metals [37]. A series of catalysts containing *para*-substituted triphenylphosphine ligands that differ in electronic character but not steric size were investigated. A plot of Hammett constant σ_p versus $\log(k_1)$ shows that a linear free energy relationship exists between phosphine dissociation rate constant and electronic parameter. More electron-withdrawing phosphines dissociate at faster rates than electron-donating phosphines ($\rho = 1.70$), demonstrating a strong link between initiation rates and phosphine donor ability.

Comparison of k_{-1}/k_2 did not reveal a linear relationship for phosphine rebinding (k_{-1}). However, these differences are considerably smaller than the differences in k_1 , suggesting that faster initiators should be faster catalysts. Accordingly, the relative reaction rates for ROMP and RCM indicate that improved initiation does lead to increased catalytic rate.

Additional studies have demonstrated that phosphine scavengers should improve the steady-state concentration of the 14e⁻ intermediate, thereby increasing the rate of reaction. However, as is the case with the bis(phosphine) catalysts, removing phosphine from the reaction also serves to increase competing decomposition.

1.9.3.3

Thermal Decomposition of Ruthenium Catalysts

Decomposition of the second-generation catalysts is less well studied than the first-generation catalysts. However, several salient features have been elucidated. First, these catalysts are extremely stable, in both the solid state and in solution, even in comparison to robust catalysts such as **1** [12, 25, 26, 28, 38]. A possible explanation is that the bulky H₂IMes ligand may hinder bimolecular decomposition. This exceptional thermal stability renders investigation of decomposition difficult. Second, the decomposition of **2** can be suppressed by addition of phosphine, indicating that phosphine dissociation precedes decomposition [12, 38]. As with the first-generation catalysts, the rate of decomposition is related to the rate of initiation; the slow rate of PCy₃ dissociation from **2** likely contributes to the low decomposition rate. Third, as with the bis(phosphine) complexes, decomposition of the methylenide (H₂IMes)(PCy₃)(Cl)₂Ru=CH₂ is not inhibited by phosphine. In fact, the methylenide decomposes at roughly the same rate that it initiates. Finally, additional decomposition pathways are also possible in these systems. For example, C–H insertion products of **2** (as well as with other transition metal complexes containing NHC ligands) have been identified [16, 39], suggesting the presence of transient metal hydrides. Suppression of hydride formation can be critical to the success of reactions involving olefins that are prone to isomerization. As such, the identification of decomposition products and pathways remains the subject of ongoing efforts.

1.9.3.4

Decomposition in the Presence of Functional Groups

The second-generation catalysts exhibit generally high stability to a range of functional groups but are susceptible to oxidative decomposition. For example, the use of non-degassed solvents leads to formation of benzaldehyde, as was seen with the first-generation catalysts. Likewise, prolonged exposure to methanol can also be detrimental and results in formation of carbonyl hydride species [16]. Coordinating solvents can be problematic, by competing with olefinic substrate for metal coordination. However, substrate functionality, which is present in considerably lower

concentration than solvent, is very well tolerated, particularly in comparison to Mo-based complexes. Accordingly, the Ru-based systems have seen widespread use in both small and complex molecule synthesis.

1.9.3.5

Other Second-Generation Ruthenium Catalysts

A variety of related second-generation catalysts have been investigated in olefin metathesis reactions (Figure 1.9-7). Hoveyda reported a second-generation tethered catalyst (**13**) [40]. Somewhat surprisingly, **13** initiates faster than **2**, yet **9** initiates slower than **1**. After a single turnover with olefinic substrate, **2** and **13** provide the same propagating species. Consequently, these catalysts are expected to have similar catalytic ability, although the rates using **13** should be somewhat faster, due to

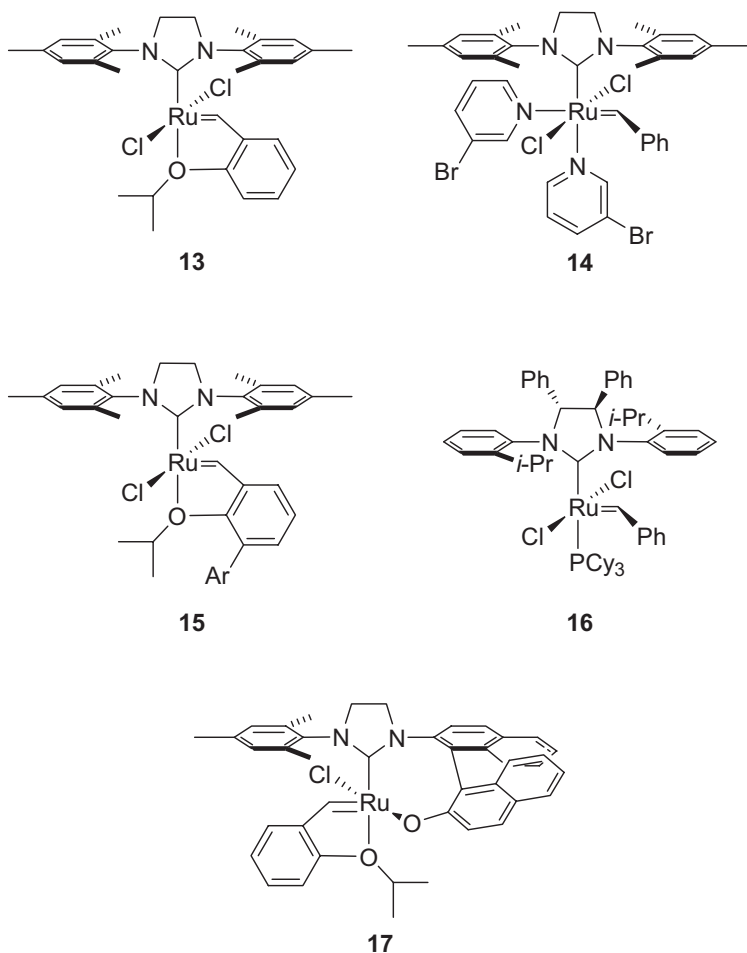


Fig. 1.9-7. Other second-generation catalysts.

increased initiation and the absence of a strongly coordinating ligand. It is therefore noteworthy that **13** provides considerably higher yields in CM reactions of acrylonitrile in comparison to **2** [41]. This observation suggests that the presence or absence of a strong donor ligand can be critical in certain reactions. By attenuating the donor strength of the L ligands, high yields can be obtained in acrylonitrile CM. For example $(\text{H}_2\text{IMes})(3\text{-Br-pyridine})_2(\text{Cl})_2\text{Ru}=\text{CHPh}$ (**14**) and **13** provide similar results. Because the rates of initiation and decomposition appear to be linked, complex **14** decomposes faster than other second-generation catalysts. Importantly, however, **14** can be prepared in one synthetically simple transformation from **2**, whereas the synthesis of **13** requires several steps [42].

A series of catalysts with similar tethers has been reported (**15**, Figure 1.9-6) [43]. Consistent with earlier discoveries, this study demonstrated that initiation can be improved by increasing steric bulk of the dissociating ligand.

Complex **13** and related dendrimeric catalysts were developed as a means for catalyst recycling [40]. These tethered catalysts are thought to proceed by a mechanism similar to the bis(phosphine) complexes [22]. Other recyclable “boomerang” catalysts that link the ruthenium complex through a polystyrene support have been reported [44, 45].

Asymmetric olefin metathesis reactions have become possible with the advent of suitable catalysts. Initial work from the Grubbs group focused on the use of Mo-based catalysts [46]. The groups of Schrock and Hoveyda reported significant improvements over the initial discovery [47]. The higher stability and functional group tolerance of Ru catalysts relative to Mo prompted the design of Ru catalysts for asymmetric olefin metathesis. These efforts culminated in the discovery of **16** (Figure 1.9-6), which can perform RCM with ee's of up to 90% [48]. In each case, the geometry of the intermediates is not known, yet this information is crucial to the design of new chiral catalysts. Although DFT studies suggest that olefin binds *trans* to the NHC ligand [49], experimental results are more easily explained with side-on binding of olefin. This remains an active area of investigation, particularly because of the potential of using mild metathesis conditions to obtain enantio-enriched products. A Ru-based catalyst with a different chiral motif was recently reported (**17**, Figure 1.9-6), and this catalyst is active for asymmetric ROM of strained olefins [50].

1.9.4

Conclusions

A variety of ruthenium olefin metathesis catalysts have been prepared and investigated. A number of mechanistic issues remain to be elucidated, including direct observation of the 14e⁻ intermediate, the nature of Ru–NHC bonding, decomposition pathways, and the geometry of intermediates. Of these, the geometry of the intermediates is the least understood, although this information is crucial for the design of catalysts that allow high Z-olefin formation and enantioselective metathesis processes. Investigations in this area will undoubtedly drive the next discov-

eries in olefin metathesis and will yield new insights into the mechanism of this process.

References

- DIAS, E. L.; NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.
- SANFORD, M. S.; ULMAN, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.
- WU, Z.; NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503.
- LOUIE, J.; GRUBBS, R. H. *Organometallics*, **2002**, *21*, 2153.
- (a) HINDERLING, C.; ADLHART, C.; CHEN, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2685. (b) ADLHART, C.; HINDERLING, C.; BAUMANN, H.; CHEN, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204. (c) ADLHART, C.; VOLLAND, M. A. O.; HOFMANN, P.; CHEN, P. *Helv. Chim. Acta* **2000**, *83*, 3306. (d) VOLLAND, M. A. O.; ADLHART, C.; KIENER, C. A.; CHEN, P.; HOFMANN, P. *Chem. Eur. J.* **2001**, *7*, 4621.
- TALLARICO, J. A.; BONITATEBUS, P. J.; SNAPPER, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157.
- CHATTERJEE, A. K.; MORGAN, J. P.; SCHOLL, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
- SANFORD, M. S.; LOVE, J. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
- COLLMAN, J. P.; HEGEDUS, L. S.; NORTON, J. R.; FINKE, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, 1987.
- SANFORD, M. S. Ph.D. Thesis, California Institute of Technology, 2001.
- ULMAN, M.; BELDERRAIN, T. R.; GRUBBS, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689.
- ULMAN, M.; GRUBBS, R. H. *J. Org. Chem.* **1999**, *64*, 7202.
- (a) NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858.
- (a) DROUIN, S. D.; YAP, G. P. A.; FOGG, D. E. *Inorg. Chem.* **2000**, *39*, 5412. (b) DROUIN, S. D.; ZAMANIAN, F.; FOGG, D. E. *Organometallics* **2001**, *20*, 5495.
- OLIVAN, M.; CAULTON, K. G. *Inorg. Chem.* **1999**, *38*, 566.
- TRNKA, T. M. Ph. D. Thesis, California Institute of Technology, 2003.
- NGUYEN, S. T. Ph.D. Thesis, California Institute of Technology, 1996.
- HANSEN, S. M.; ROMINGER, F.; METZ, M.; HOFMANN, P. *Chem. Eur. J.* **1999**, *5*, 557.
- HANSEN, S. M.; VOLLAND, M. A. O.; ROMINGER, F.; EISENTRAGER, F.; HOFMANN, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1273.
- DIAS, E. L.; GRUBBS, R. H. *Organometallics* **1998**, *17*, 2758.
- CHANG, S.; JONES, L.; WANG, C.; HENLING, L. M.; GRUBBS, R. H. *Organometallics* **1998**, *17*, 3460.
- KINGSBURY, J. S.; HARRITY, J. P. A.; BONITATEBUS, P. J., JR.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.
- (a) BOURISSOU, D.; GUERRET, O.; GABBAY, F. P.; BERTRAND, G. *Chem. Rev.* **2000**, *100*, 39. (b) ARDUENGO, A. J. *Acc. Chem. Res.* **1999**, *32*, 913. (c) HERRMANN, W. A.; KOCHER, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163.
- (a) WESKAMP, T.; SCHATTENMANN, W. C.; SPIEGLER, M.; HERRMANN, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490. (b) Erratum to Ref. 24a: WESKAMP, T.; SCHATTENMANN, W. C.; SPIEGLER, M.; HERRMANN, W. A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 262.
- SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

- 26 HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSON, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.
- 27 WESKAMP, T.; KOHL, F. J.; HIERINGER, W.; GLEICH, D.; HERRMANN, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416.
- 28 Ding: M. SCHOLL, S. DING, C. W. LEE, GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953.
- 29 CHATTERJEE, A. K.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 1751.
- 30 CHATTERJEE, A. K.; SANDERS, D. P.; GRUBBS, R. H. *Org. Lett.* **2002**, *4*, 1939.
- 31 CHOI, T. L.; CHATTERJEE, A. K.; GRUBBS, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.
- 32 LOVE, J. A.; SANFORD, M. S.; DAY, M. W.; GRUBBS, R. H. **2002**, *J. Am. Chem. Soc.*, **2003**, in press.
- 33 BIELAWSKI, C. W.; GRUBBS, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903.
- 34 FÜRSTNER, A.; ACKERMANN, L.; GABOR, B.; GODDARD, R.; LEHMANN, C. W.; MYNOTT, R.; STELZER, F.; THIEL, O. R. *Chem. Eur. J.* **2001**, *7*, 3236.
- 35 DINGER, M. B.; MOL, J. C. *Adv. Synth. Catal.* **2002**, *344*, 671.
- 36 (a) FERNANDEZ, A. L.; REYES, C.; WILSON, M. R.; WOSKA, D. C.; PROCK, A.; GIERING, W. P. *Organometallics* **1997**, *16*, 342. (b) WOSKA, D. C.; PROCK, A.; GIERING, W. P. *Organometallics* **2000**, *19*, 4629. (c) DRAGO, R. S.; JOERG, S. *J. Am. Chem. Soc.* **1996**, *118*, 2654. (d) JOERG, S.; DRAGO, R. S.; SALES, J. *Organometallics* **1998**, *17*, 589.
- 37 ALYEA, E. C.; SONG, S. *Comments Inorg. Chem.* **1996**, *18*, 189.
- 38 ULMAN, M. Ph.D. Thesis, California Institute of Technology, 2000.
- 39 HUANG, J. K.; STEVENS, E. D.; NOLAN, S. P. *Organometallics* **2000**, *19*, 1194.
- 40 GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
- 41 (a) RANDL, S.; GESSLER, S.; WAKAMATSU, H.; BLECHERT, S. *Synlett* **2001**, *3*, 430. (b) GESSLER, S.; RANDL, S.; BLECHERT, S. *Tetrahedron Lett.* **2000**, *41*, 9973.
- 42 LOVE, J. A.; MORGAN, J. P.; TRNKA, T. M.; GRUBBS, R. H. *Angew. Chem. Int. Ed.*, **2002**, *41*, 4035.
- 43 (a) WAKAMATSU, H.; BLECHERT, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 794. (b) WAKAMATSU, H.; BLECHERT, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.
- 44 AHMED, M.; ARNAULD, T.; BARRETT, A. M. G.; BRADDOCK, D. C.; PROCOPIOU, P. A. *Synlett* **2000**, *1007*.
- 45 JAFARPOUR, L.; NOLAN, S. P. *Org. Lett.* **2000**, *2*, 4075.
- 46 FUJIMURA, O.; GRUBBS, R. H. *J. Org. Chem.* **1998**, *63*, 824.
- 47 (a) HOVEYDA, A. H.; SCHROCK, R. R. *Chem. Eur. J.* **2001**, *7*, 945. (b) HULTZSCH, K. C.; JERNELIUS, J. A.; HOVEYDA, A. H.; SCHROCK, R. R. *Angew. Chem. Int. Ed.* **2002**, *41*, 589. (c) ALEXANDER, J. B.; LA, D. S.; CEFALO, D. R.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041.
- 48 SEIDERS, T. J.; WARD, D. W.; GRUBBS, R. H. *Org. Lett.* **2001**, *3*, 3225.
- 49 See chapter by P. CHEN in this volume.
- 50 VAN VELDHIJZEN, J. J.; GARBER, S. B.; KINGSBURY, J. S.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954.

1.10

Intrinsic Reactivity of Ruthenium Carbenes

Christian Adlhart and Peter Chen

1.10.1

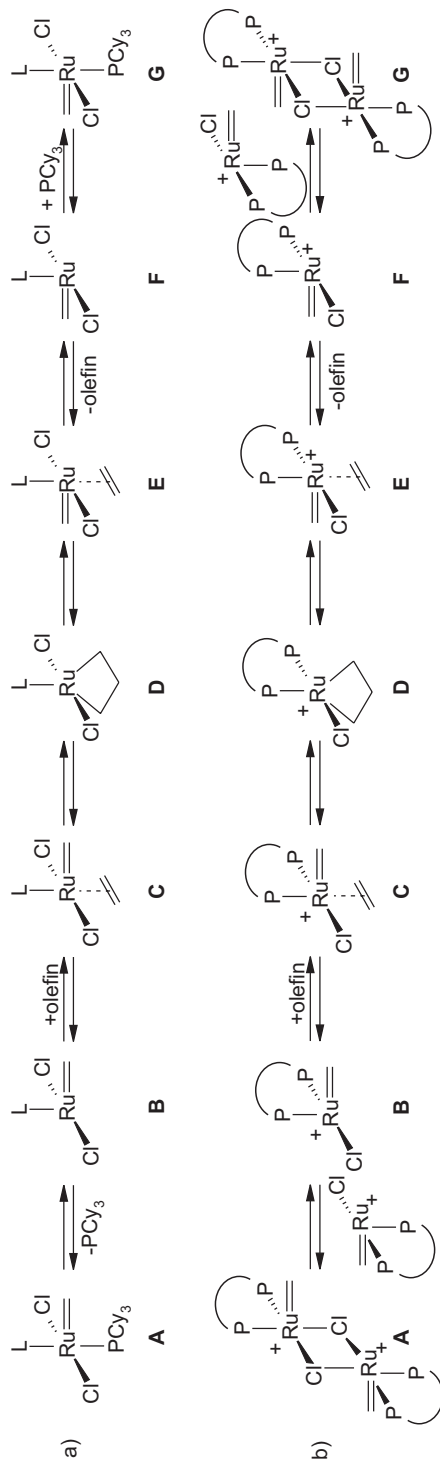
Introduction

The discovery and progressive improvement of Ru-based metathesis catalysts [1–12] has made an understanding of the mechanistic basis for the high activity of considerable theoretical as well as practical interest.

Our mechanistic investigations were performed in the gas phase on cationized variants of the ruthenium carbene precursors [8–12], applying mass spectrometric methods. Tandem mass spectrometry is probably the best tool for deconvolution of multi-step reaction mechanisms with several subsequent pre-equilibria into individual steps. Furthermore, exchange of substituents can be done easily by preparing an equilibrating mixture of desired complexes and picking the individual complex of interest out of the mixture by its mass. To complete our understanding of the mechanism, the gross topology of the energy surfaces has been computed using combined quantum mechanical and force-field methods. Calculations also provide structural information for the individual intermediates that may not be directly accessible by mass spectrometric techniques.

We will begin with an introduction of electrospray ionization mass spectrometry, followed by an overview of different kinds of olefin metathesis reactions that can be performed in the gas phase: acyclic cross-metathesis (ACM), ring-opening metathesis polymerization (ROMP), and ring-closing metathesis (RCM). Finally, mechanistic investigations are presented where the three key factors determining the activity of metathesis catalysts are discussed; solution-phase pre-equilibria determining the activation efficiency of the catalysts, pre-equilibria during the catalyst turnover caused by backbiting, and differences of the topology of the overall potential surface determining the commitment of the catalyst.

In Scheme 1.10-1, the most likely mechanisms for both the Grubbs-type and Hofmann-type ruthenium-carbene-catalyzed olefin metathesis are shown. A detailed discussion will be presented later; however, in order to facilitate readability, a three-parameter notation with the purpose of denoting all intermediate complexes in the reaction cycle systematically is introduced here. The first number is the principal number of the starting complex according to Figure 1.10-1. Second, all



Scheme 1.10-1. Accepted dissociative mechanism for olefin metathesis according to experiments [13–15] and calculations [10, 16–20].

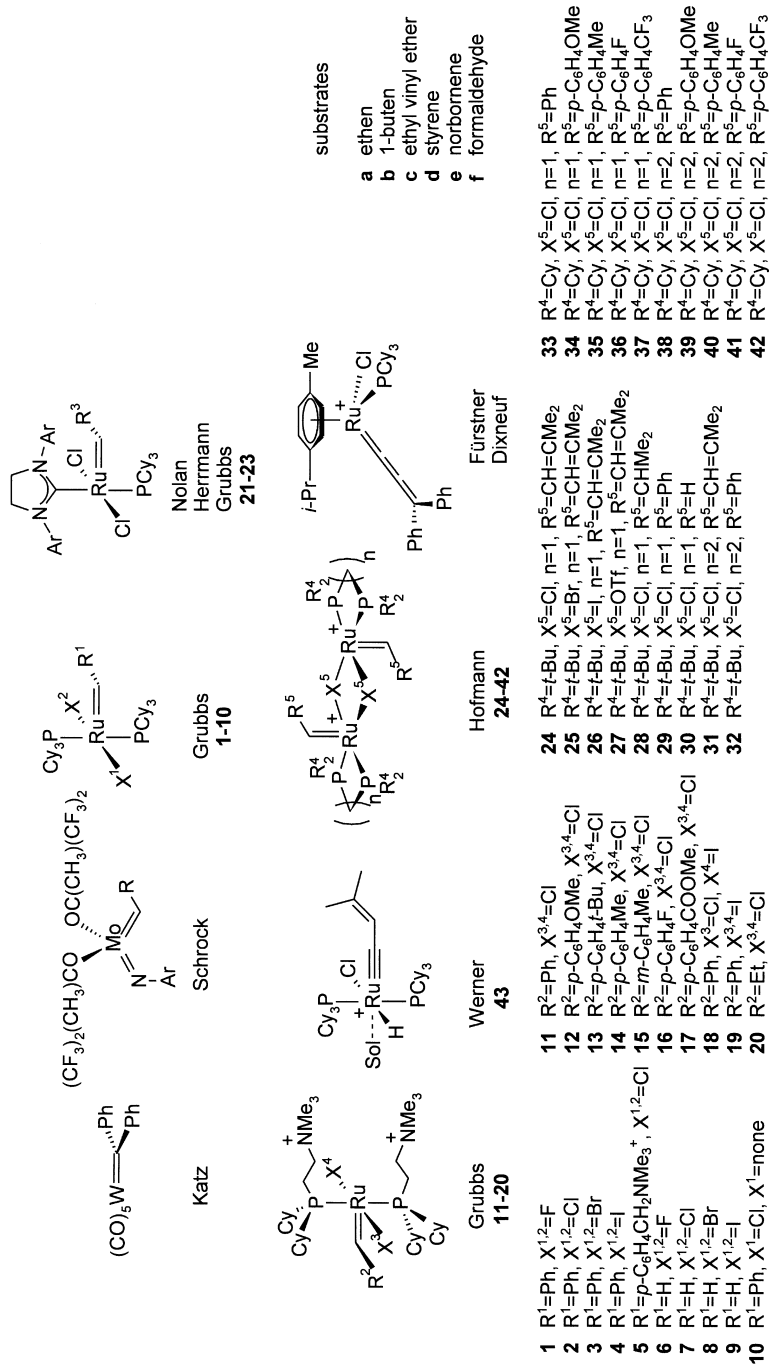


Fig. 1.10-1. The discovery and progressive improvement of Ru-based metathesis catalysts [1–7] and their cationized variants [8–12].

intermediates arising from catalysis by ruthenium-carbene complexes are denoted with the additional letters **A** to **G**, according to Scheme 1.10-1, and finally, an additional letter, **.a** (ethene), **.b** (1-butene), **.c** (ethyl vinyl ether), **.d** (styrene), **.e** (norbornene), and **.f** (formaldehyde), denotes the olefinic substrate. The notation is useful because solution-phase investigations are mostly done with pre-catalyst **A**, whereas in our gas-phase work reactivity of the active 14-electron species **B** has been investigated.

1.10.2

Electrospray Ionization Mass Spectrometry (ESI MS) of Transition Metal Complexes

In recent years, the efforts of many investigators have led to new techniques for producing ions of species too large and complex to be vaporized without substantial decomposition. The most successful techniques developed so far are electrospray ionization (ESI) and matrix-assisted laser desorption (MALDI), which have revolutionized the analysis of biomolecules. The inventors were awarded the Nobel Prize in chemistry in 2002. The application of ESI MS to transition metal complexes, however, has remained relatively untouched [21–23].

1.10.2.1

Electrospray Ionization

The electrospray ionization method allows the transfer of ions in solution into the gas phase under very mild conditions. It therefore is not an ionization method in the same sense as electron impact, where a neutral precursor is ionized by removal of an electron. The electrospray process – the dispersion of liquids by the aid of an electric field – originates from the paint and coating industry. In 1968 Dole and coworkers [24] demonstrated the capability of electrospray to transfer macromolecular ions into the gas phase. Their analytical method, however, was limited by the use of a drift time spectrometer. In 1984 Fenn et al. [25, 26] coupled an electrospray source with a mass spectrometer and applied it to the mass spectrometry of biomolecules [27]; they realized that proteins could be electrosprayed without denaturation. Non-covalent receptor–ligand complexes and even viruses remain intact [28].

Macromolecular biomolecules are typically electrosprayed as a series of peaks with different charge of up to 30 positive charges and have to be deconvoluted to their native mass. This happens through aggregation of a different number of H^+ , Li^+ , and Na^+ ions from buffer salts in the electrospray solution to the polar groups in the proteins. Multiple charging allowed biomolecules to be handled with an m/z range typical for a quadrupole mass filter. Organometallic complexes, on the other hand, are small compared to biomolecules and appear in a defined charged state (up to two positive or negative charges) at their intrinsic charge (e.g., $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}\}^{2+}$ **11**, $z = +2$, $m/z = 415$) without aggre-

gation of buffer salt ions. ESI of organometallic complexes has been reviewed in [22] in general, as well as in specific applications [23].

Although ESI is now in common use in biological applications, its component processes and mechanisms, especially the dispersion of the sample liquid into charged droplets and the formation of gas phase ions from those droplets, are poorly understood (single ion in droplet theory [24, 29] or ion evaporation model [30–33]). Both of these processes are very complex, depending strongly on an intricate interplay between variables such as flow rate, applied field, and solution properties including conductivity, surface tension concentration, dielectric constant and viscosity, as well as the structure and confirmation of the analyte molecules. The most likely mechanism closely resembles field desorption, which also gives very “soft” ionization.

1.10.2.2

Tandem Mass Spectrometry

The continuous ESI source is ideally coupled with a continuously operating mass filtering device such as a quadrupole mass filter, as shown in a block diagram for our ESI mass spectrometer (Figure 1.10-2). Its general features will be described briefly. After being generated, gas-phase ions pass the heated capillary region where further desolvation takes place. At the differentially pumped skimmer region, they are passed from atmospheric pressure into high vacuum. A perpendicular field that serves primarily to guide the ions into the off-axis skimmer can be used as an adjustable parameter to induce collisions with ambient gas and to control the mode of fragmentation, which allows removal of weakly bound ligands to generate coordinative unsaturated complexes for reactivity studies. The ions then “diffuse” through the radio frequency (rf) 24-pole, where the ions are either thermalized by collisions with inert gas or reacted with reagent gas at a pressure of up to 100 mTorr. After the first quadrupole mass filter (Q1), ions can be accelerated ($-200 \dots 200$ eV) into the rf octopole collision cell (O2), where they can again be

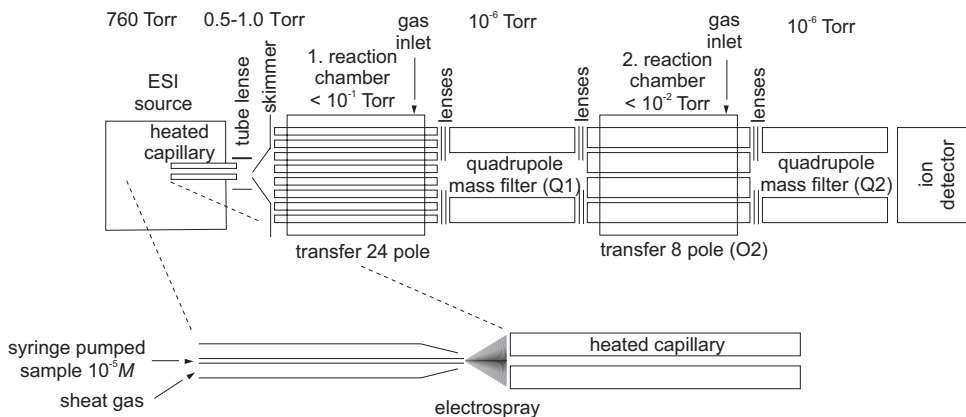


Fig. 1.10-2. Block diagram of the modified Finnigan MAT TSQ 700 ESI tandem MS.

reacted with neutral gas as reactant at a pressure of up to 10 mTorr. Collisions can energize ions to facilitate gas-phase reactions. Under appropriate conditions, the barrier can even be measured. Ions are finally detected with an electron multiplier. The tandem mass spectrometer allows four principal operational modes: (1) the mass analyzer mode where either Q1 or Q2 are scanned while the other quadrupole mass filter serves in a transmission mode as ion guide; (2) the daughter ion mode where Q1 is used as a “purifying” filter to allow the transmission of ions with a specific mass-over-charge (m/z) ratio and Q2 is scanned to analyze the products formed by reactions of the purified ions with reaction gas in O2; (3) the parent scan where Q1 is scanned while Q2 filters a specific m/z , which allows us to scan for *a priori* unknown ions that react to a known product; and (4) the neutral difference scan where Q1 and Q2 are scanned parallel with a specified $\Delta m/z$ to look for ions that undergo a specific change in mass (e.g., addition of a norbornene $\Delta m/z = 94$ unit for different ROMP catalyst).

1.10.2.3

Reaction Conditions in the Collision Cell of the Tandem ESI MS

Monte Carlo simulations using Langevin theory [34–36] for the probability of a collision indicate that, under the reaction conditions employed here, ion molecule reactions occurred under thermal conditions at 343 K with ≈ 5000 collisions with the reactant gas in O2. The simulated retention time for the ions in the collision cell was ≈ 1 –10 ms, depending on the pressure of the collision gas and the initial kinetic energy of the ions (Figure 1.10-3). The number of collisions in the 24-pole

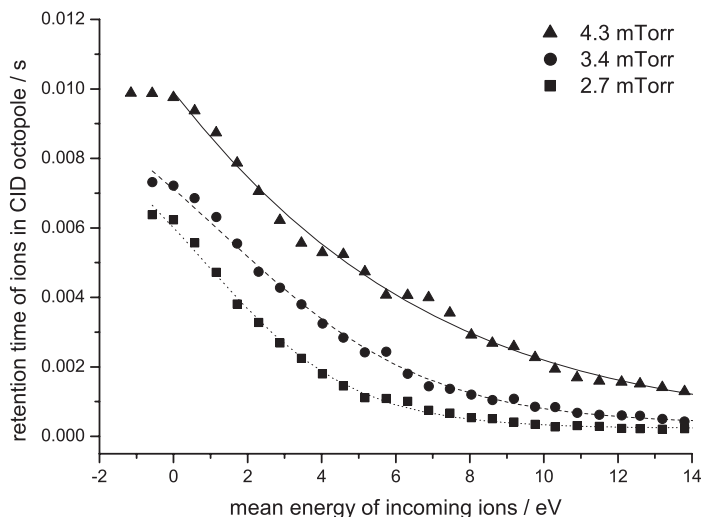


Fig. 1.10-3. Simulation of the mean ion retention time in the gas-filled octopole collision cell as a function of incident ion energy and gas pressure for the reaction of ruthenium-benzylidene complex **11** with 1-butene.

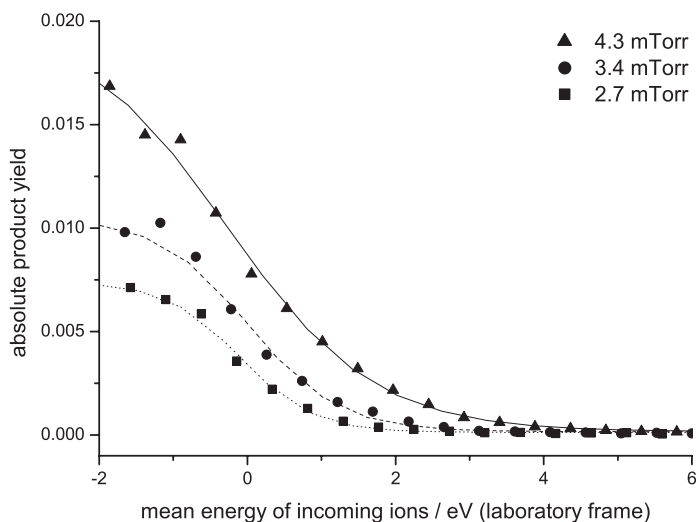


Fig. 1.10-4. Absolute product yields for the reaction **11** and 1-butene as a function of the incident kinetic energy of **11** (laboratory frame) and the pressure of 1-butene in the octopole collision cell.

(O1) can be an order of magnitude or more higher. It should be noted that the collision frequency of 10^6 – 10^7 sec^{-1} facilitates the simulation of condensed-phase chemistry in the gas phase. Efficient thermalization of chemically activated intermediates produced in exothermic reactions leads to solution-phase-like behavior.

The plots of measured yield against the same pressure and incident energy parameters are shown in Figure 1.10-4. The product yield at nominal negative energy of the incoming ions (laboratory frame) arises from the high-energy tail of the energy distribution in O₂, which is broadened from ≈ 1 eV in an rf-only scanning mode to ≈ 2 eV in the daughter ion mode. Because the Monte Carlo simulation realistically reproduces the experimentally determined retention time of the ions in the gas-filled octopole, the absolute collision number from the simulation, up to ≈ 5000 collisions per ion in O₂, can be taken as reliable. Furthermore, because the curves in Figures 1.10-3 and 1.10-4 are approximately parallel, one can reduce the measured product yield to a probability of reaction per collision of between 10^{-4} and 10^{-5} . These are high reaction efficiencies for organometallic reactions, although they are very low compared to standard ion molecule reactions [37].

Besides the enhancement of rate – which is caused by attractive ion dipole or ion-induced dipole interactions common for all gas-phase reactions – gas-phase transition metal complex-catalyzed reactions, according to our experience, parallel solution-phase behavior, and reactivity trends observed for different catalysts can be extrapolated to solution phase.

While there certainly is an entropic preference for dissociative processes and intramolecular reactions in the gas phase, no gross differences in reactivity trends

comparable to those seen for gas-phase ion molecule reactions, such as nucleophilic substitution reactions or carbonyl addition reactions, were found [23, 38–40]. The major difference between transition metal-catalyzed reactions and “classical” ion molecule reactions is a non-polar transition state. This is especially true for olefin metathesis, which can be considered as a pericyclic reaction. Therefore, any electrostatic effects that are different between gas phase and solution phase will affect reactants, transition states, and products similarly, leading to relative rates between different transition metal complexes that parallel their solution-phase relative rates. This has been shown computationally [17] and experimentally for the ruthenium-carbene systems. The absolute gas-phase rates, however, are enhanced by several orders of magnitude due to favorable ion-induced dipole interactions and the absence of a solvent cage.

1.10.3

General Reactivity of Ruthenium Carbene Complexes in the Gas Phase

The purpose of the gas-phase experiments presented here was to establish empirically the extent to which gas-phase olefin metathesis reactivity of ruthenium-carbene complexes known to perform olefin metathesis in solution resembles behavior in solution. This is of particular interest because especially gas-phase ion molecule reactions, such as nucleophilic substitution or carbonyl addition reactions, diverged significantly in their solution- and gas-phase behavior [38–40]. Although, according to our experience, transition metal-catalyzed reactions behave similarly in solution and in gas phase [23], some differences such as the gas-phase formation of an unprecedented iridiaphosphoran were found upon investigations of C–H activation by Ir(III) complexes [41, 42]. Finally, experiments were performed to investigate whether any mechanistic information obtained in gas-phase olefin metathesis reactions was transferable to a solution-phase mechanism.

We started our gas-phase investigations with the diiodide salt of the dicationic ruthenium complex **11**, originally designed by Grubbs et al. [8], to provide a water-soluble olefin metathesis catalyst. Under relatively mild desolvation conditions, i.e., a tube lens potential of 44 V, the mass spectrum consists of the intact catalyst, as is shown in Figure 1.10-5. As the tube lens potential was increased stepwise to 150 V, the intensity of a peak due to **11B** without the second phosphane increased at the expense of that for **11A**. Two further peaks arising from monocations **18B** and **19B** indicated that one or two of the chlorides had been replaced in solution by one or two iodide counter ions of the ammonium groups.

1.10.3.1

Dissociative Mechanism

When 1-butene was used as collision gas in O₂, the daughter ion peak of dicationic **11** ($m/z = 415$) decreased, collision-induced dissociation (CID) of one phosphane ligand ($m/z = 284$) was observed and the peak of the monocationic 14-electron

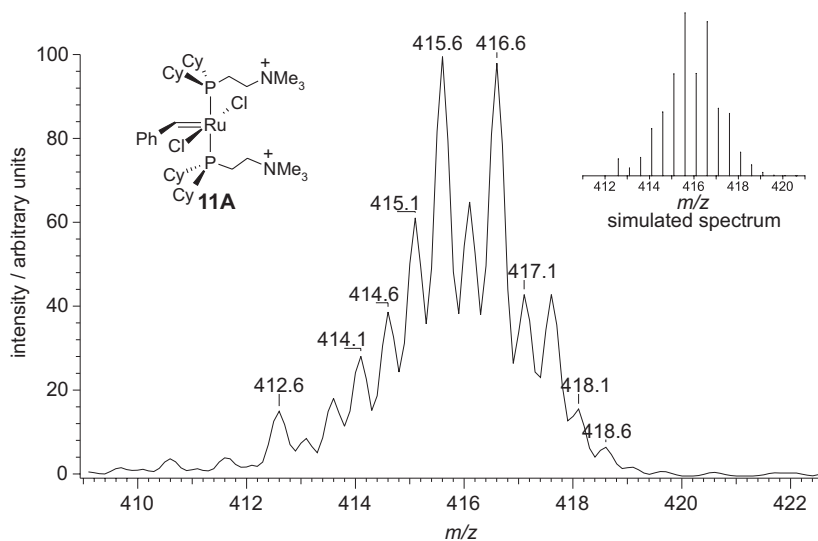


Fig. 1.10-5. ESI MS spectrum of the dicationic ruthenium complex **11A** taken from a 10^{-5} M solution of **11A** in CH_2Cl_2 at 44 V tube lens potential.

complex **11B** ($m/z = 546$) appeared (Figure 1.10-6). A further peak that corresponds to the mass of the 14-electron propylidene complex **11F.b** indicates that the benzylidene complex **11B** has reacted by an acyclic metathesis reaction with 1-butene to produce the propylidene complex **11F.b** and styrene, which is a neutral species and therefore not observable. Although the prototype reaction has been studied mass spectrometrically for several simple metal carbenes ($[\text{Mn}=\text{CH}_2]^+$, $[\text{Fe}=\text{CH}_2]^+$ and $[\text{Co}=\text{CH}_2]^+$ [43–45]), this was the first observation of olefin metathesis in the gas phase by a complex that performs the same reaction in solution and the first observation of the 14-electron complex, which had already been discussed as an intermediate in olefin metathesis by Grubbs-type ruthenium-carbene complexes [13]. To our knowledge, it was also the first organometallic gas-phase ion molecule reaction in which the charged group is not directly involved in the reaction but served only as a handle to transfer the complex into the gas phase. The separation of the charge from the reactive center is well known for investigation of distonic radical ions [46]. A thorough investigation of the spectrum in Figure 1.10-6 indicates the absence of a peak corresponding to the dicationic bis phosphane propylidene complex **11G.b** ($m/z = 391$), which would be the product for an associative 18-electron mechanism for the olefin metathesis reaction. This together with independent daughter ion experiments of **11B** ($m/z = 546$), which can be “prepared” by harsh desolvation conditions in the tube lens region (>150 V) and which reacted readily with 1-butene, strongly favored the dissociative mechanism (Scheme 1.10-1) which is currently accepted (*vide infra*).

Interestingly, we failed to detect a peak corresponding to any of the possible intermediates **11C.b–11E.b** with $m/z = 602$, although, by the logic of the mech-

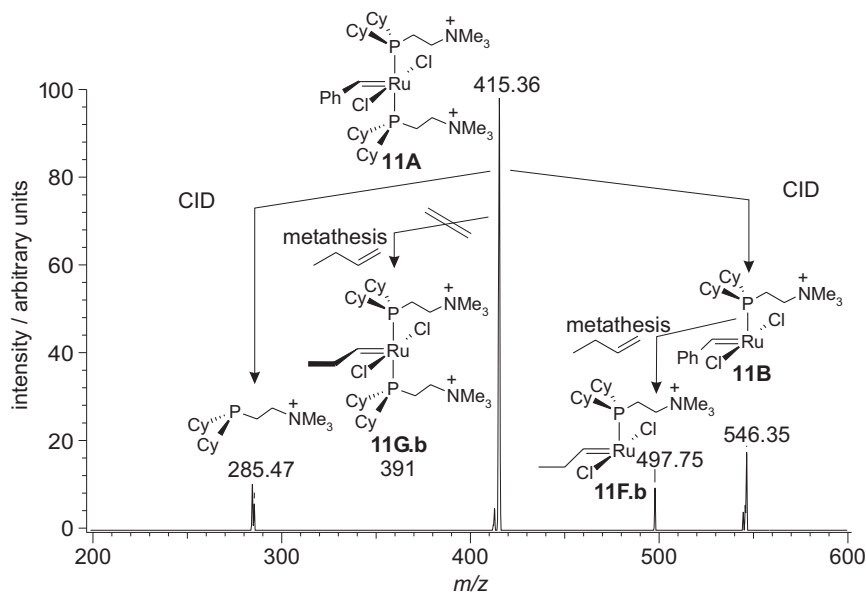


Fig. 1.10-6. Daughter ion mass spectrum taken by reaction of the mass-selected ruthenium complex **11A** ($m/z = 498$) with 1-butene.

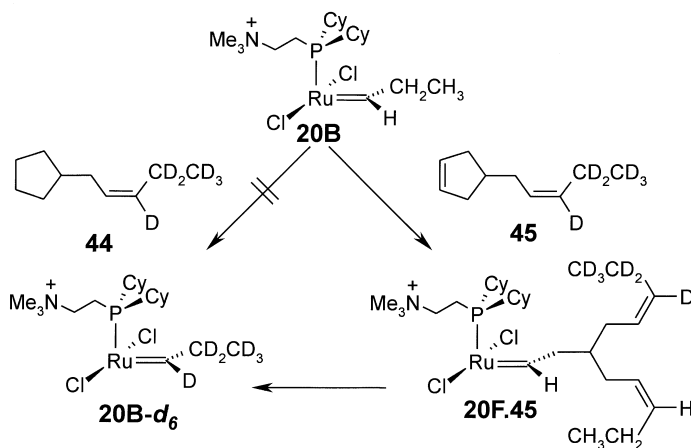
anism for olefin metathesis presented in Scheme 1.10-1, they must have been present – at least as metastable intermediates. The alternative methylene complex was absent. We believe that this represents a kinetic preference in the metathesis reaction, which becomes evident because of reaction under non-equilibrating conditions. Precisely the same kinetic preference was reported by Grubbs et al. [47]. The monocations **18B** and **19B** showed a reduced gas-phase reactivity towards 1-butene in the order **11B** > **18B** >> **19B**, which has also been reported for the reaction of the dibromides and diiodides in solution [13, 48].

We were also interested in the reaction of **11A** with formaldehyde, as it is known that ruthenium-carbene complexes do not react with carbonyl compounds [49]. A possible present kinetic barrier could, in principle, be surmounted by increasing the collision energy. Although formaldehyde did not show any reactivity towards **11A** or **11B** even at collision energies up to 50 eV, a new peak with $m/z = 590$ was formed that corresponds to the structures **11C.f–11E.f**. When the $m/z = 590$ peak was generated independently by collision with formaldehyde in the rf 24-pole and collided with argon in the CID region, it lost the mass of formaldehyde, suggesting the formation of **11C.f** rather than **11D.f** or **11E.f**.

1.10.3.2

Evidence for ROMP and RCM

While there has been evidence for ROMP in the gas phase by the fact that uptake of up to five norbornene units by $\{(H_2IMes)(Cl_2)Ru=CHC_6H_4CH_2N(CH_3)_3\}^+$ (**23**)



Scheme 1.10-2

was observed (Figure 1.10-11), a more direct test can be made with bifunctional substrates that offer the product of a ring-opening metathesis reaction the chance to undergo a non-degenerate ring-closing metathesis to an isotopically or otherwise substituted complex distinguishable from the original complex by mass (Scheme 1.10-2). In the cyclopentane analogue **44** of **45**, the more reactive cyclic olefinic site had been removed. It served as a control to exclude reactivity at the linear internal olefinic. Neither of the two possible cross-metathesis products, the propylidene-*d*₆ complex ($m/z = 504$) or the 3-cyclopentanyl-propylidene complex ($m/z = 552$), was observed for the cyclopentane case; the cyclopentene derivative **45**, on the other hand, leads to approximately 10% conversion of **20B** ($m/z = 498$) to **20B-d₆** ($m/z = 504$) (Figure 1.10-7), indicating clearly that the ring-opening metathesis of cyclopentene had occurred ($m/z = 578$) and is furthermore reversible. Similar experiments with the bifunctional substrate 5-vinylnorborn-2-ene confirmed that harsh collision conditions ($\gg 3$ eV) are needed to surmount thermochemical barriers to the reconstruction of the strained ring in norbornene.

By means of the reversibility experiments, we can argue on kinetic grounds that ring-opening metathesis polymerization (ROMP) of cyclopentene ($k_{0 \rightarrow 1} = 0.01$) and cyclohexene ($k_{0 \rightarrow 1} = 0.00$) was inefficient (in comparison to ROMP of cyclobutene [$k_{0 \rightarrow 1} = 13$] or norbornene [$k_{0 \rightarrow 1} = 15$] [14]), not because the ring-opening metathesis itself was inherently slow, but rather because the facile formation of an intramolecular π complex, favored for the longer, more flexible spacers derived from cyclopentene and cyclohexene, introduces an unfavorable pre-equilibrium and promotes an unproductive ring-closing metathesis. This conjecture finds confirmation in the direct probes for reversible ROM by the substituted cyclopentenes and norbornenes. The ROM of cyclopentene is readily reversible, while that of norbornene is not. As had been argued by Patton and McCarthy [50–52], strain release in the substrate is not the principal determinant in all but perhaps one of

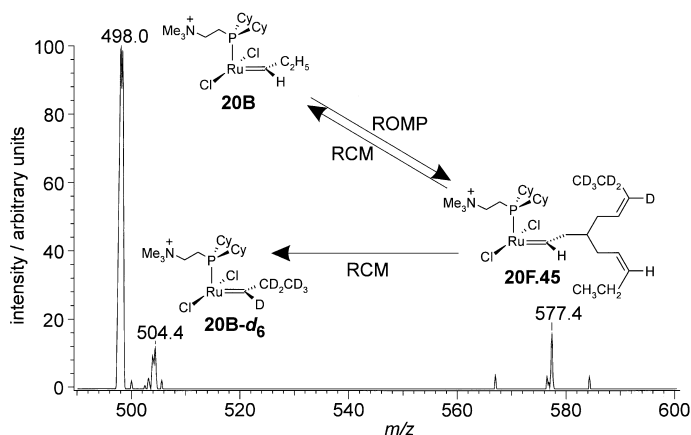


Fig. 1.10-7. Daughter ion mass spectrum taken by reaction of the mass-selected ruthenium-propylidene complex **20B** ($m/z = 498$) with 10 mTorr of 4-[(*Z*)-2-pentenyl-3,4,4,5,5,5- d_6]-cyclopentene.

the several orders-of-magnitude differences between apparent ROMP reactivity of cyclohexene and norbornene in solution. The easy intramolecular π complexation is primarily a steric effect, and concomitant ring-closing metathesis is the controlling factor.

1.10.3.3

Systematic Variation of a Common Structural Motif – Steric Effects and Halogen Effects

While in the preceding Grubbs-type catalyst **11** the charge was introduced in the phosphane ligand far from the reactive center, the presumably active 14-electron species **B** (Scheme 1.10-1) of the highly active Hofmann-type ruthenium-carbene complexes $\{[R_2P(CH_2)_nPR_2-\kappa^2P](X)Ru=CHR']_2\}^{2+}$ is intrinsically charged at the ruthenium center [10, 19, 53]. Our interest in the Hofmann-type system is explained on the one hand by the charge on the ruthenium center that may affect the previously mentioned coincidence of gas phase and solution-phase reactivity and on the other hand by the ability to study identical rather than merely similar systems in solution and in the gas phase.

One hopes that any mechanistic information obtained in the gas phase can be transferable to a solution-phase mechanism. Furthermore, a high degree of molecular diversity via simple *in situ* ligand exchange in solution combined with online “purification” [20] of the Hofmann-type catalyst was accessible for systematic studies (Figure 1.10-8).

In general the 14-electron complexes $\{[R_2P(CH_2)_nPR_2-\kappa^2P](X)Ru=CHR']^+$ and $\{(PCy_2(CH_2)_2N(CH_3)_3)(X)_2Ru=CH-m,p-C_6H_4R'\}^+$ showed comparable gas-phase

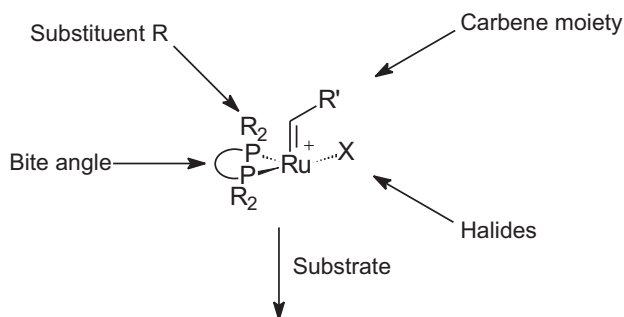


Fig. 1.10-8

reactions towards olefins, but some notable differences in reactivity have been observed. First, the reaction of **24B** with electron-poor olefins such as 1-butene was considerably slower than it was for **11B**, although **24** was known to exhibit at least 2 orders of magnitude higher solution-phase activity towards cyclooctene than **2**. Therefore, we switched to the more reactive vinyl ethers for comparative kinetic measurements of different variants of $\{[R_2P(CH_2)_nPR_2-\kappa^2P](X)Ru=CHR'\}^+$. Second, considerable amounts of one or all of the intermediates **C.c** to **E.c** were seen, as exemplified for the reaction of **35** with ethyl vinyl ether in Figure 1.10-9. Third, **24B** did not show any evidence for RCM in the ROM–RCM experiment, as described in Section 1.10.3.2, within the observable timeframe in our gas-phase experiments (≈ 10 ms). The results for systematic ligand variation on the $\{[R_2P(CH_2)_nPR_2-\kappa^2P](X)Ru=CHR'\}^+$ -motif (Figure 1.10-8), except for the carbene moiety (see “Constructing the Energy Surface After Formation of the Active Species” section), are summarized below.

Anionic ligand variation The relative reaction rates of the reaction of $\{[(dtbpm)-\kappa^2P](X)Ru=CH-CH=C(CH_3)_2\}^+$ ($dtbpm = (t-Bu)_2P(CH_2)P(t-Bu)_2-\kappa^2P$, $X = Cl$ (**24B**), Br (**25B**), I (**26B**), OTf (**27B**)) with 1-butene were 1.00, 0.4, 0.046, and 0.000. As has been reported for the Grubbs system [13, 48], the chloride ligand leads to the most active compound. Gas-phase reactivity in the Hofmann system is reduced by a factor of 20 when chloride is replaced by iodide. No reactivity towards the substrate 1-butene can be observed for triflate (OTf) under the outlined conditions. It is conceivable that bidentate coordination of the triflate ligand blocks the reactive coordination site.

Variation of phoshane ligands: Sterics Our results reveal that catalyst **38B**, with the less bulky *dcpe* ligand ($dcpe = Cy_2P(CH_2)_2PCy_2-\kappa^2P$), reacts 55 times faster with ethyl vinyl ether than does catalyst **32B**, with the more bulky *dtbpe* ligand ($dtbpe = (t-Bu)_2P(CH_2)_2P(t-Bu)_2-\kappa^2P$) [54]. This underlines the profound influence of steric demand on metathesis. Additionally, the equilibrium constant for the adduct complex **38C.c** of the *dcpe* complex **38B** and ethyl vinyl ether is considerably larger than for the sterically more demanding *dtbpe* **32C.c**. We find a differ-

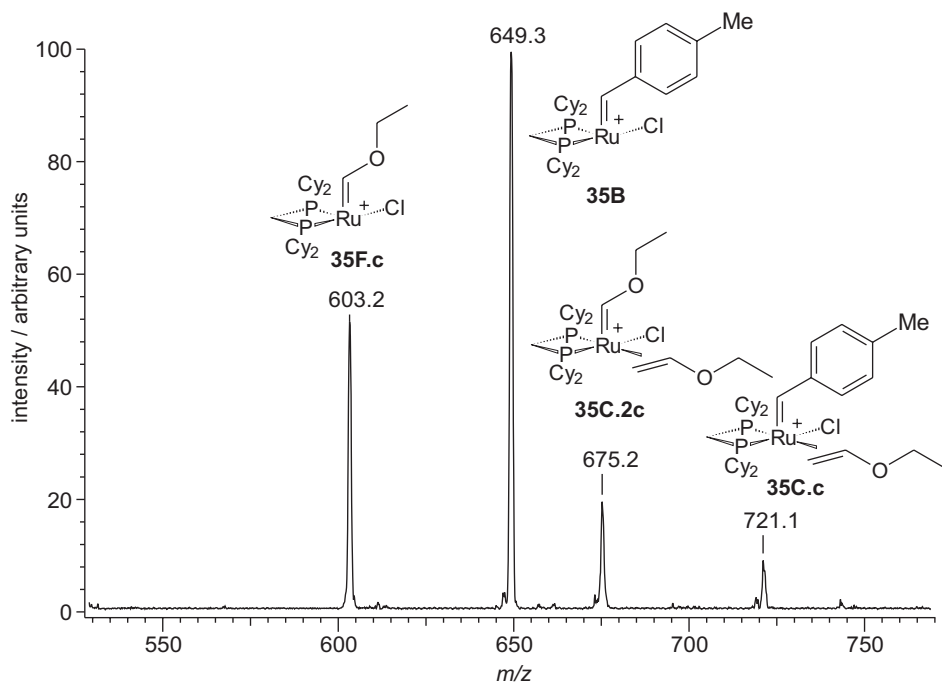


Fig. 1.10-9. Daughter ion mass spectrum taken by reaction of the mass-selected ruthenium-*p*-methyl-benzylidene complex **35B** ($m/z = 649$) with ethyl vinyl ether as reaction gas in the CID cell.

ence of a factor of 50 for the pre-equilibria between *dcpe* and *dtbp*. The coincidence of the difference in binding of the olefinic substrate with the difference in reaction rate indicates that the substrate-catalyst-binding pre-equilibrium is the principal factor affecting reactivity, at least within this structural class. For acyclic metathesis, enhanced π -complex formation increases rate. As will be shown later, the same phenomenon decreases overall rate in ROMP.

Variation of phoshane ligands: The chelating angle (bite angle) Variation of the ligand bite angle (P-Ru-P angle) from 74° to $\approx 180^\circ$ has a profound effect on the reactivity towards different olefinic substrates, as was demonstrated for $\{[R_2P(CH_2)_nPR_2-\kappa^2P](X)Ru=CHR']^+$ ($R = t\text{-Bu}$, Cy; $n = 1, 2, 3$). For the *t*-Bu ligands, enlarging the bite angle from 74° to 86° decreases the rate by a factor of 5 for 1-butene and up to a factor of 100 for ethyl vinyl ether [10, 19, 20, 55]. The same trend was observed in the case of the Cy ligands. The extreme case with a P-Ru-P angle of $\approx 180^\circ$ is realized in $\{(PCy_3)_2(Cl)Ru=CHPh\}^+$ (**10**) [56], which shows no reactivity (neither formation of adduct nor metathesis product) towards olefinic substrates under our gas-phase reaction conditions. For **10** we presume that the bite angle affects the reversible isomerization to a hydrido carbyne upon abstraction of one chlorine [9, 57–59], which is not reactive in olefin metathesis. In

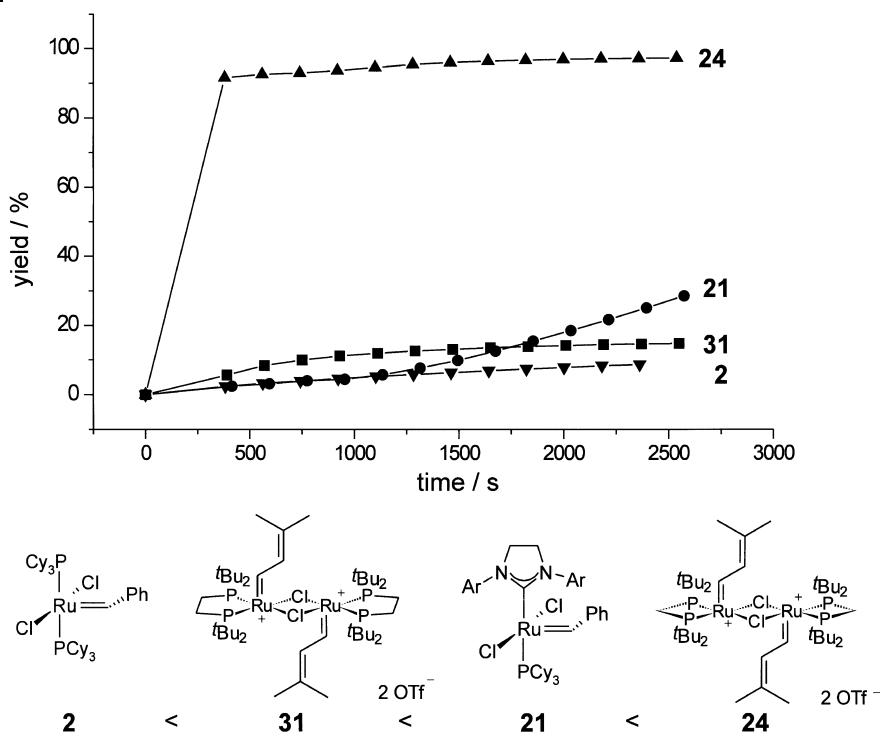


Fig. 1.10-10. ROMP of cyclooctene in solution. Comparison of polycyclooctenamer production as followed by ^1H NMR spectroscopy. $T = 298\text{ K}$; $0.5\text{ mL CD}_2\text{Cl}_2$; $c(\text{cyclooctene})$: $c(\text{Ru}) = 12,500:1$ [20, 53].

summary, the overall metathesis rate is reduced drastically for increased ligand bite angles.

Variation of phosphane ligands – Rates in solution Comparison of the combinatorial accessed relative gas-phase reactivity of $\{[\text{R}_2\text{P}(\text{CH}_2)_n\text{PR}_2-\kappa^2\text{P}](\text{X})\text{Ru}=\text{CHR}'\}^+$ with the solution-phase reactivity of **24** and **31** revealed the same trends, with the dtbpm complex being faster than the dtpbe complex (Figure 1.10-10).

1.10.3.4

Conclusions

Many features that appear in solution-phase metathesis reactions of ruthenium-carbene complexes also appear in the gas phase, e.g., the prerequisite of phosphane dissociation in **11** [60]; the formation of the propylidene complex for the reaction with 1-butene, which is interpreted as the kinetic product [47]; the observation of ROMP and RCM; and higher reactivity for the chloride complexes than

for the iodide complexes [13, 48]. The only exception is the absolute rate by which olefin metathesis occurs in the gas phase; acceleration factors of about 10^4 were observed for both acyclic metathesis and ROM [14].

From these similarities we conclude that mechanistic information obtained in the gas phase can be transferred to the overall solution-phase mechanism.

1.10.4

Three Key Factors that Determine the Activity of Metathesis Catalysts

While it has been demonstrated that gas-phase reactivity of ruthenium-carbene complexes can be extrapolated to the solution phase and that mass spectrometric techniques are capable of exploring the parameter space influencing the reactivity of ruthenium-carbene complexes (*vide supra*), the logical target of reactivity studies has to be extraction of the physical basis for catalyst activity from that data. The overall catalyst activity has been deconvoluted into three factors that – although depending on each other – determine overall activity; pre-equilibria prior to turnover, pre-equilibria during the turnover, and commitment.

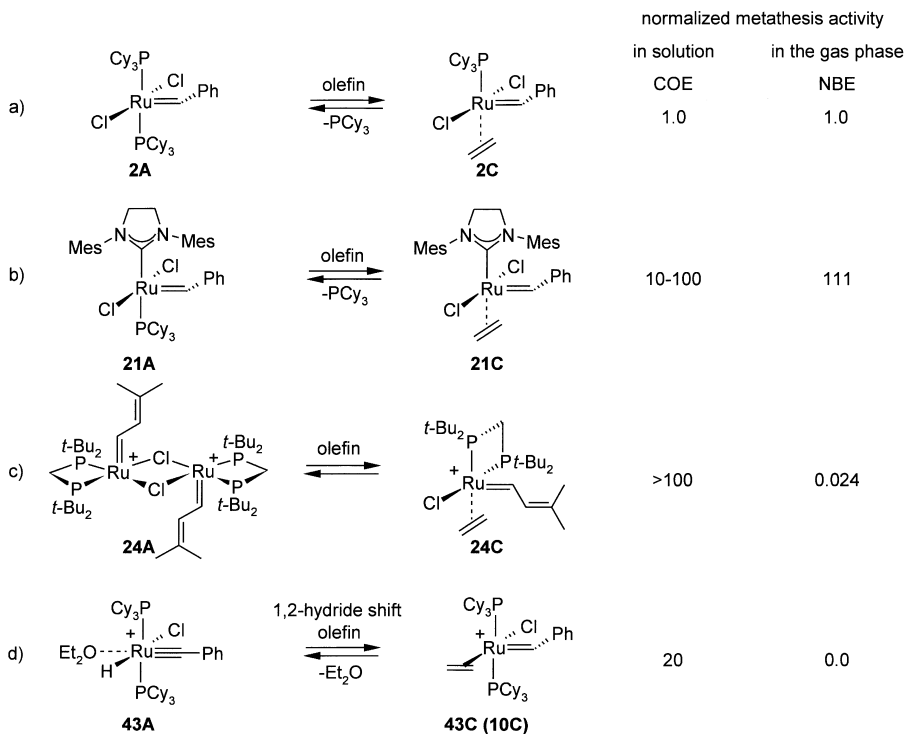
1.10.4.1

Solution-Phase Pre-Equilibria: Activation

Relative solution-phase reactivities of different ruthenium pre-catalysts for olefin metathesis of cyclooctene (COE) are shown in Scheme 1.10-3 and are compared to the gas-phase rates of the presumably active species **B** towards norbornene (NBE). While the solution-phase rates reflect a combination of initiation and propagation, gas-phase rates are direct measurements of the intrinsic reaction rates. The fact that intrinsic gas-phase rates and solution-phase rates do not correlate at all can be explained only by a different fraction of active species present in solution, which in turn comes from a different equilibrium constant K_{AC} (assuming a fast pre-equilibrium).

The difference in the relative gas-phase rate of **24B** with NBE (0.024) compared with its relative solution-phase rate (>100 , COE) (entry c in Scheme 1.10-3) is explained by a factor of ≈ 4000 more-favorable activation step of **24** to form the monomeric **24B**. With a ΔG^\ddagger (298 K) of $19.11 \text{ kcal/mol}^{-1}$ for the loss of PCy_3 from **2A** to form **2B** [61], ΔG^\ddagger for the formation of **24B** from its dimer can be estimated to be $\Delta G^\ddagger \approx 14 \text{ kcal/mol}^{-1}$.

The Werner-type ruthenium-carbyne initiators **43** [9] presumably form an active carbene species by a 1,2 hydrogen shift (entry d in Scheme 1.10-3). While we do not want to state whether the active species in the Werner systems is a 14-electron [58] or 16-electron carbene complex **10** [56], we can state that a complex corresponding to $\{(\text{PCy}_3)_2(\text{Cl})\text{Ru}=\text{CHPh}\}^+$ (**10**) or its hydrido carbyne isomer **43** did not show any gas-phase olefin metathesis reactivity in our experiments [20, 56]. It is also the only one of the three complexes for which the activation step for the solution-phase reaction is also present in the gas-phase experiment.



Scheme 1.10-3. COE = cyclooctene, NBE = norbornene. For solution-phase data, see entry (b), Figure 1.10-10, and [20], (for COD, see [62]) and entry (c)), Figure 1.10-10 and [10, 20], and entry (d) [9].

1.10.4.2

Pre-Equilibria During the Turnover: Backbiting

The equilibrium constant for π complexation effects the overall rate When the relative rates for the acyclic olefin metathesis of ethyl vinyl ether by $\{[(\text{dtbpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CHPh}\}^+$ (**32B**) and $\{[(\text{dcpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CHPh}\}^+$ (**38B**) are compared with each other, a factor of 50 higher reactivity k_{obs} was found for the dcpe system. The same factor of 50 in favor of the dcpe system was found for the amount of π complex **C**, which stands in a fast and barrier-less [16] pre-equilibrium with **B** and free olefin (K_{BC}) [20, 63]. Assuming a rate-determining step k_{CD} , the ratio of the constants K_{BC} accounts for essentially all of the difference in rate for the metathesis reaction (Eq. (1)), and consequently the activation energy for the step **C** to **D** must be the same for **32C** and **38C**. According to the different K_{BC} , the π complexation of ethyl vinyl ether to **38B** is ≈ 2.7 kcal mol $^{-1}$ more favorable than to **32B**.

$$k_{\text{obs}} = k_{\text{CD}}[\text{C}] = (k_{\text{BC}}/k_{\text{CB}})(k_{\text{CD}})[\text{B}][\text{olefin}] = K_{\text{BC}}k_{\text{CD}}[\text{B}][\text{olefin}] \quad (1)$$

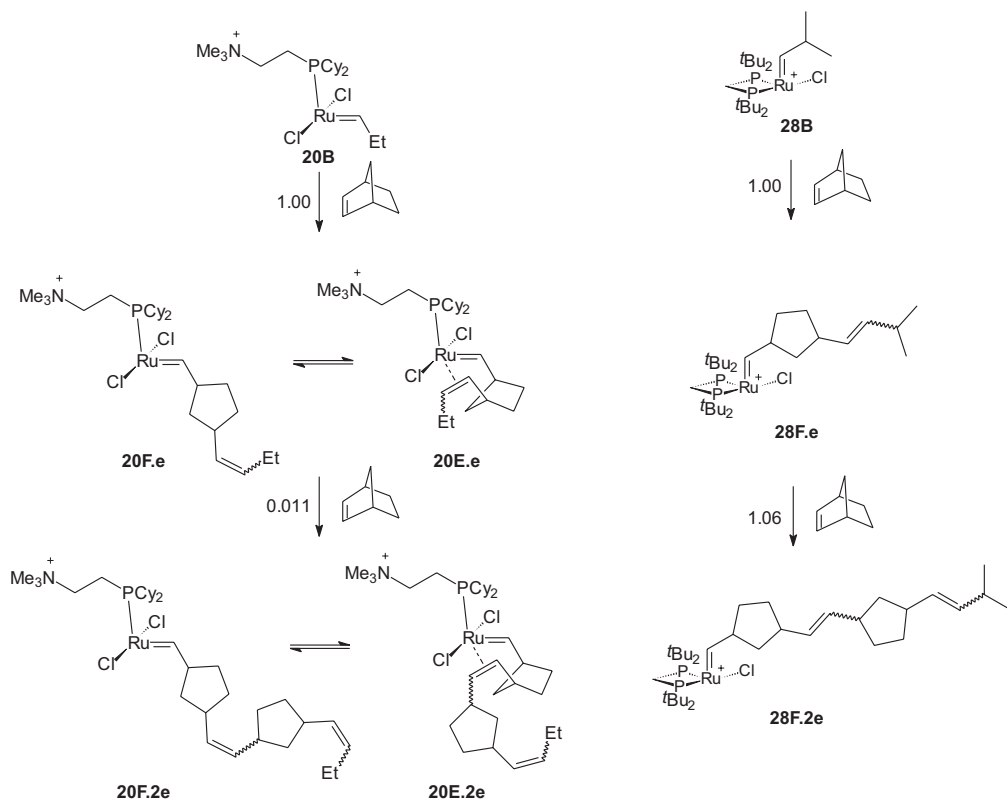
A similar conclusion can be drawn from results where the metathesis activity of $\{(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHC}_6\text{H}_4\text{CH}_2\text{N}(\text{CH}_3)_3\}^+$ (**5B**) and $\{(\text{H}_2\text{IMes})(\text{Cl})_2\text{Ru}=\text{CHC}_6\text{H}_4\text{CH}_2\text{N}(\text{CH}_3)_3\}^+$ (**23B**) with ethyl vinyl ether is compared with the appearance of a signal that has to be attributed to any of the intermediate structures **C.c** to **E.c** (presumably **C** [63]). Whereas the total rates for **5B** and **23B** are 0.002(1) and 0.077(5), the abundance for the intermediates is 0.0005(3) and 0.757(7). This means that while **23B** reacts by a factor of ≈ 40 faster with ethyl vinyl ether than does **5B**, there is a factor of ≈ 1500 more intermediate species present. If the intermediate really was the π complex **C**, the fast pre-equilibrium $\text{B} \rightleftharpoons \text{C.c}$, K_{BC} would accelerate the cross-metathesis reaction of ethyl vinyl ether by **23B** compared with **5B** more than the actual rate k_{CD} , because the rate-limiting step would be a factor of $\approx 1/30$ slower for **23B** (Eq. (1)).

A notable correlation between the peak intensity of the presumed π complex with the overall olefin metathesis reactivity was also found for the reaction of $\{[\text{R}_2\text{P}(\text{CH}_2)_n\text{PR}_2-\kappa^2\text{P}](\text{X})\text{Ru}=\text{CHR}'\}^+$ ($\text{R} = t\text{-Bu}$, Cy ; $\text{R}' = \text{CHCH}=\text{CMe}_2$, Ph ; $n = 1, 2, 3$) with both 1-butene and ethyl vinyl ether [20], where the fastest complexes in acyclic metathesis showed the highest tendency to form a π adduct with the olefin substrate. The only exceptions were the reactions of dtbpm and dtbpe complexes with 1-butene. For the ROMP reaction of the dtbpm and dcpm ($\text{dcpm} = \text{Cy}_2\text{P}(\text{CH}_2)\text{PCy}_2-\kappa^2\text{P}$) systems with norbornene, a second and, depending on the residues, even a third insertion of norbornene was observed only for the dtbpm systems, even though dcpm is much more reactive towards norbornene in the first step. Moreover, no second insertion was detectable for any complex upon reaction with cyclopentene. An interpretation considering the backbiting of a propagating polymer will be given in the following section.

Kinetic analysis of initiation and propagation rates for ROMP of norbornene: Backbiting With mass spectrometric techniques we can also resolve the intensity for every living oligomer peak. Numerical analysis assuming first-order kinetics on the peak intensities for the polymerization of norbornene by **11B** has revealed a different reactivity for the first polymerization step (k_1) and the subsequent polymerization steps ($k_{2\dots n}$) of a factor of $k_1/k_{2\dots n} \approx 70$ [14] and $k_1/k_{2\dots n} \approx 90$ for the propylidene complex **20B**. The reduction in $k_{2\dots n}$ compared with k_1 in each system can be attributed to different carbenes in the starting complexes (benzylidene (**11B**) and propylidene (**20B**)) as well as a difference in the turnover rate.

The latter difference is due to the possibility of the formation of an intramolecularly bound π complex with the propagating polymer, which is not possible in the initial benzylidene or propylidene complexes. It acts as a pre-equilibrium that reduces the amount of the active open-chain, 14-electron complex by a factor of ≈ 90 (Scheme 1.10-3). Justification for the assumption of an intramolecular π complex can also be drawn from X-ray structures of ruthenium-carbene [64] and tungsten-carbene [65, 66] complexes with intramolecular π coordinated olefin at the γ or δ position of the carbenes.

Interestingly, when the same kinetic analysis for the gas-phase polymerization of norbornene is applied to the dtbpm complex **28**, whose initial isobutylidene group



Scheme 1.10-4. Backbiting of the growing polymer chain in the Grubbs system **20B** slows down insertion of additional norbornene, whereas backbiting seems to be absent in the Hofmann dtbpm **28B** system.

is rather close to the carbenes formed upon polymerization, one sees no deviation for the reactivity in the first and the subsequent propagation steps $k_1/k_{2...n} = 0.94$, suggesting that no such intramolecular π complex is present in this case (Scheme 1.10-4). This is consistent with the size of the dtbpm ligands, which also adversely affected the formation of intermolecular π complexes.

In order to achieve a direct comparison between the first- and second-generation ruthenium carbene catalysts, $\{(PCy_3)(Cl)_2Ru=CHC_6H_4CH_2N(CH_3)_3\}^+$ (**5B**) and $\{(H_2IMes)(Cl)_2Ru=CHC_6H_4CH_2N(CH_3)_3\}^+$ (**23B**) were reacted with norbornene in the gas phase in the CID region. The experimental and numerical fit data and a spectrum in segmented mode are shown in Table 1.10-1 and Figure 1.10-11. While it is not yet clear why the propagation ($k_{2...n}$) for **5B** should proceed faster than the initiation (k_1), the reduction of $k_{2...n}/k_1$ by a factor of 10 for **23B** can be attributed to a difference in the degree of intramolecular π -complex formation by the growing polymer chain.

Tab. 1.10-1. Experimental intensities for the polymer peaks I_n are given normalized to the total intensity I_{tot} of all peaks. Each intensity I_n is the result of 10 measurements, and the error is given at 95% confidence based on a t distribution. Initiation rate k_i and propagation rate k_p are calculated based on first-order kinetics using the given intensities.

	$5B_{exp}$	$5B_{calc}$	$23B_{exp}$	$23B_{calc}$
I_0/I_{tot}	0.982(43)	0.9817	0.121(4)	0.1206
I_1/I_{tot}	0.017(1)	0.0173	0.402(12)	0.4022
I_2/I_{tot}	0.001(0)	0.0009	0.298(6)	0.2899
I_3/I_{tot}	—	0	0.152(4)	0.1304
I_4/I_{tot}	—	0	0.025(1)	0.0429
I_5/I_{tot}	—	0	0.002(0)	0.0111
k_1/t		0.019(1)		2.115(77)
$k_{2...n}/k_1$		6		0.598

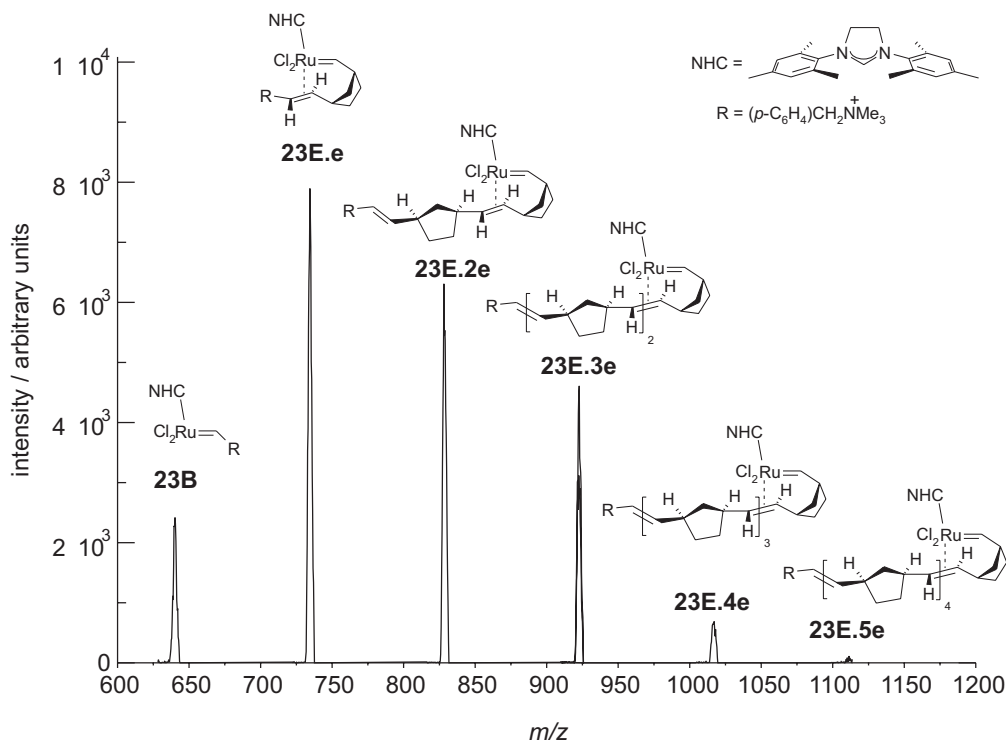


Fig. 1.10-11. Gas-phase ROMP of norbornene with **23**; segmented scan mode. $k_i = 2.115$ and $k_p = 0.598 \times k_i$.

Computational evidence for backbiting By means of combined QM/MM calculations (*vide infra* [67]), we were able to obtain a rough estimate of the relative energies of the intramolecularly bound π complexes compared to their open-chain conformers for the reaction of **7**, **22**, and **30** with norbornene. The obtained en-

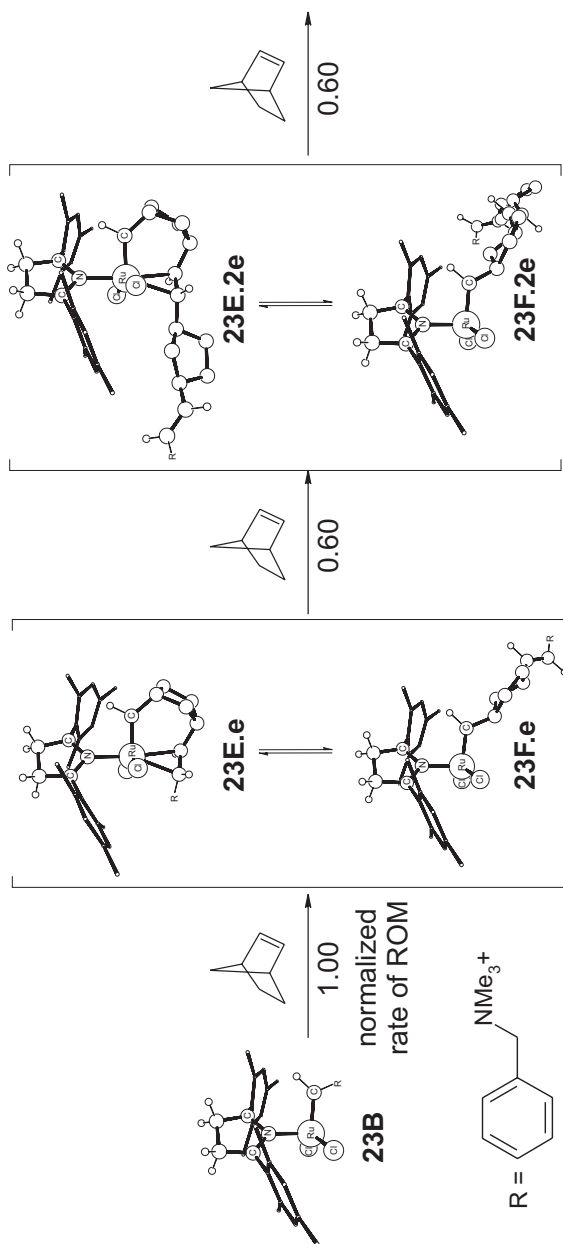
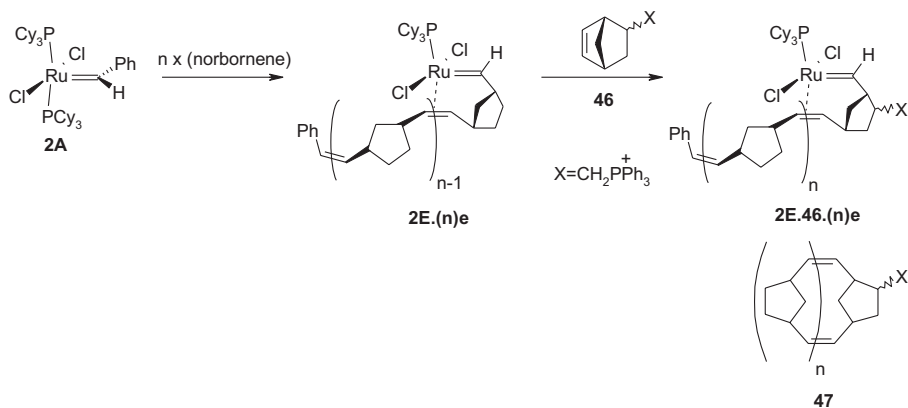


Fig. 1.10-12 Formation of an intramolecularly bound π complex prevents the subsequent polymerization event.

ergies $\Delta E_{QM/MM}$ (F.e–E.e) for the first (and second) insertion step were 2.66 (2.11, *trans/iso*), 4.61 (3.43 *trans/syn*), and -0.11 (-2.87 *trans/syn*) kcal mol $^{-1}$, respectively [68]. The negative $\Delta E_{QM/MM}$ for **30** is consistent with the absence of any indication of backbiting, and the more positive $\Delta E_{QM/MM}$ for **22** compared with **7** is consistent with a smaller $k_{2...n}/k_1$ for these systems. Interestingly for **22**, the N-heterocyclic carbene ligand, which is usually considered to be sterically large [15], does not significantly prevent the formation of an intramolecular π complex (Figure 1.10-12). One presumes that the weaker π acidic NHC ligand [69, 70] (relative to a phosphane) leaves the ruthenium more willing to bind a “soft” olefinic ligand.

Direct probe for the resting state in solution: Fishing the resting state from solution The identification of the active species or even the resting state of the active catalytic cycle, as opposed to the precatalyst and any other related complexes that may be simultaneously present, is nearly always a challenging task. As has been elegantly demonstrated by Halpern [71], the most abundant complex in solution need not be a part of the most favorable catalytic cycle; in fact, it may present a dead end. Moreover, mechanistic considerations can suggest several active species that may be present. A method by which their *a priori* different levels of activity or selectivity could be quantitatively assayed would be of great utility. We have represented a methodology that can both identify and assay catalytically active species in solution for the olefin metathesis reaction of (PCy $_3$) $_2$ (Cl) $_2$ Ru=CHPh **2** with norbornene by selectively transferring them to the mass spectrometer after trapping with a “labeled” substrate [72].

Because electrospray transfers charged species from solution to the gas phase, a reaction that derivatizes active species with a charge becomes a selective probe. For ROMP of norbornene by **2**, a cationized norbornene derivative **46** was used as a probe and added (0.1 equivalent relative to **2**) after 15 min to the reaction mixture of **2** and 5 equivalents of norbornene. The solution was diluted and directly electrosprayed (Scheme 1.10-5 and Figure 1.10-13).



Scheme 1.10-5

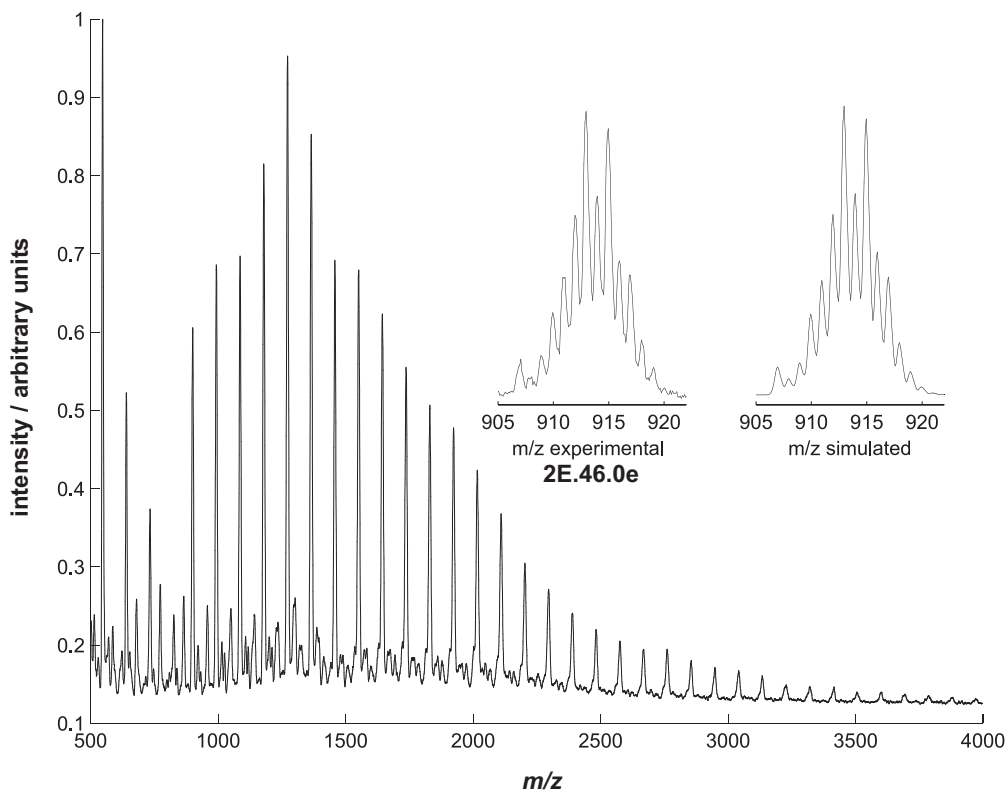


Fig. 1.10-13. ROP of 5 equivalents of norbornene with **2** and a cationized norbornene **46** as selective probe. The polymer distribution with $n = 0$ starts at $m/z = 911$. The two insets show the experimental and

computed isotope distribution for one of the oligomer peaks, which indicate, along with the mass, that the complex has one ruthenium, one phosphine, two chlorines, and one unit of the cationized norbornenes.

As mentioned previously, only charged species, either cationic or anionic, depending on whether the spectrometer is run in positive ion or negative ion mode, are transferred to the gas phase. Accordingly, the mass spectra correspond to the selective detection of the catalyst-bound, charge-labeled substrate (the selective probe). The observed species should represent the resting state of the complex involved in the catalytic cycle; as for a neutral catalyst and cationized substrate, only those complexes that bind and incorporate the substrate are detected. The mass spectrum in Figure 1.10-13 confirms that, subsequent to initiation, the catalytic cycle proceeds through the monophosphane complex without further significant involvement of a bis-phosphane complex, i.e., the resting state of the catalyst in ROP is the monophosphane complex as opposed to the bis-phosphane resting state in acyclic olefin metathesis. This is also supported by comparison of the induction period of ADMET of 1,9-decadiene, where $(\text{H}_2\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$

reached its maximum activity only after 200 s (45 °C) [73], which can be interpreted as time delay for full activation of $(\text{H}_2\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$ by loss of phosphane (known to be the rate-limiting step [15]) and some NMR evidence for the presence of a monophosphane species for ROMP of norbornene by **2** [74]. On the left-hand side of Figure 1.10-13, a second series of small peaks with a spacing of 94 can be observed. These peaks correspond according to m/z to the ring-closing metathesis products **47** of the living charge-labeled polymer (Scheme 1.10-5). The broad distribution of macrocycles ranging from 2 to ≈ 13 norbornene units suggests resting states for ROMP of norbornene by **2**, where any one of the newly formed double bonds intramolecularly coordinates to the ruthenium center of the 14-electron complex **2B.c**.

1.10.4.3

Catalyst Commitment: Potential Surface

The original expectations for a higher activity of the second-generation ruthenium-carbene complexes were based on the idea that the *trans*-coordinated, electron-rich *N*-heterocyclic carbene ligand would facilitate the dissociation of the phosphane ligand and therefore increase the fraction of the active 14-electron species and consequently increase the overall catalyst activity. Spin polarization transfer experiments by Grubbs et al. [15, 61] of free and bound phosphane, however, revealed exactly the opposite, i.e., a lower barrier for phosphane dissociation in the first-generation ruthenium-carbene catalysts and a higher barrier in the second generation. The explanation for the indeed higher activity of the second-generation catalyst was found in a higher fraction of active species reacting in the product direction (high catalyst commitment, Figure 1.10-14, right) compared to the first-generation catalysts, where a higher fraction of active species is trapped by free phosphane instead of entering the catalytic cycle (low catalyst commitment, Figure 1.10-14, left). The exact identity and energy of the highest barrier in the direction of the product-forming steps were not accessible by these spin polarization experiments. However, they can be studied in the gas phase.

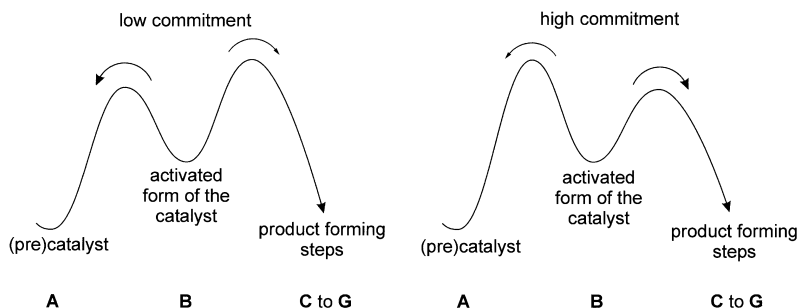


Fig. 1.10-14

Constructing the energy surface after formation of the active species As has already been demonstrated (see Section 1.10.3.1), it is possible by means of our gas-phase experiments to study the reactivity of intermediates **B** (Scheme 1.10-1) independently of any preceding pre-equilibrium $A \rightleftharpoons B$. Furthermore, small changes of the electronic properties of **11B** by introduction of substituted benzylidene ligands for reactivity studies, as have been reported for **2A** [47], could easily be done either in the mass spectrometer itself, by acyclic cross-metathesis of **11B** with substituted styrenes [36] in the rf 24-pole, or by means of *in situ* preparation and online purification in the mass spectrometer as has been done for **33** and **35** [20]. The reactivity of the online-generated complexes could be directly studied in the collision cell of the mass spectrometer. Secondary isotope effects of the α carbene hydrogen were accessible in analogy. These experiments start with the 14-electron intermediates and therefore should be sensitive to the presence of barriers on the reaction coordinate subsequent to phosphane dissociation.

Linear free-energy relationships and isotope effects Substituted ruthenium monophosphane complexes $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)(\text{Cl})_2\text{Ru}=\text{CH-}m,p\text{-C}_6\text{H}_4\text{R}'\}^+$ ($\text{R} = \text{H}$ (**11B**), OMe (**12B**), $t\text{-Bu}$ (**13B**), $p\text{-Me}$ (**14B**), $m\text{-Me}$ (**15B**), $p\text{-F}$ (**16B**), and $p\text{-COOMe}$ (**17B**)) have been prepared in the gas phase by reaction of **11B** with a variety of substituted styrenes in the rf 24-pole, and their relative reactivity with 1-butene and norbornene has been recorded [36].

Importantly, norbornene reacts with the parent ruthenium monophosphane complex much faster than does 1-butene. A plot of the logarithm of the relative rates for **11B**–**17B** reacting with 1-butene or norbornene against Hammett σ parameters [75] is linear for both reactions (Figure 1.10-15). For the reaction of **11B**–**17B** and 1-butene, $\rho = 0.69 \pm 0.10$, indicating a modest acceleration of the acyclic metathesis reaction by electron-withdrawing groups on the aryl group of the substituted ruthenium benzylidene. For the reaction of **11B**–**17B** and norbornene, on the other hand, $\rho = -0.08 \pm 0.09$, indicating essentially no electronic influence on the rate of the particular ring-opening metathesis reaction. Paquette et al. [76] reported a set of experiments in which they studied the electronic effects of substituted 1,7,9-trienes on the RCM rate of $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}$ **2** and also found rate enhancement by electron-withdrawing groups.

In analogy, substituent effects for the gas-phase reaction of substituted Hofmann-type ruthenium-carbene complexes $\{[(\text{dcpm})\text{-}\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{R}\}^+$ ($\text{R} = \text{H}$ (**33B**), OMe (**34B**), Me (**35B**), F (**36B**), CF_3 (**37B**)) and $\{[(\text{dcpe})\text{-}\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{R}\}^+$ ($\text{R} = \text{H}$ (**38B**), OMe (**39B**), Me (**40B**), F (**41B**), CF_3 (**42B**)) with ethyl vinyl ether have been recorded on *in situ* prepared complexes [20]. For the correlation of their relative reactivity with Hammett σ parameters [75], $\rho = 0.23 \pm 0.17$ and $\rho = 0.69 \pm 0.39$. This is consistent not only with the already demonstrated acceleration of the olefin metathesis reaction by electron-withdrawing groups for **11B**–**17B** but also with a larger dependence on electronic effects for the slower reacting series. It should be noted here that some deviation, such as the enhanced reactivity of the *para* fluoro-substituted complexes, was systematic for four differ-

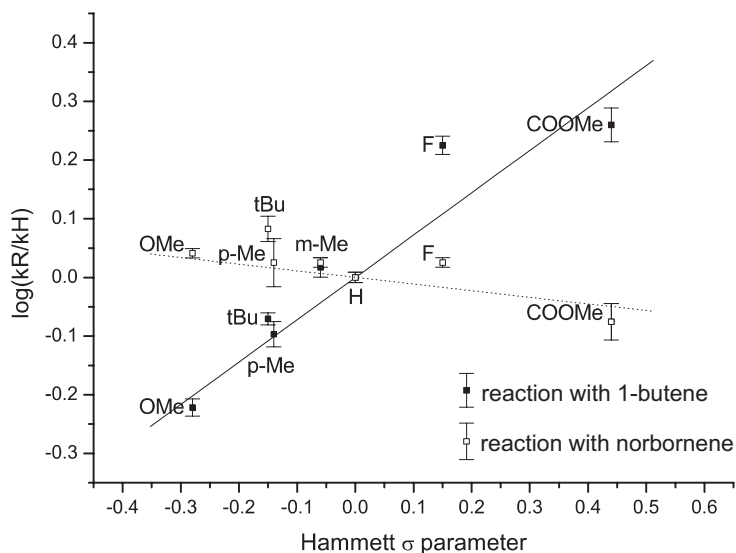


Fig. 1.10-15. Hammett plot for the relative rates of **11B–17B** with 1-butene (solid rectangles) and norbornene (empty rectangles).

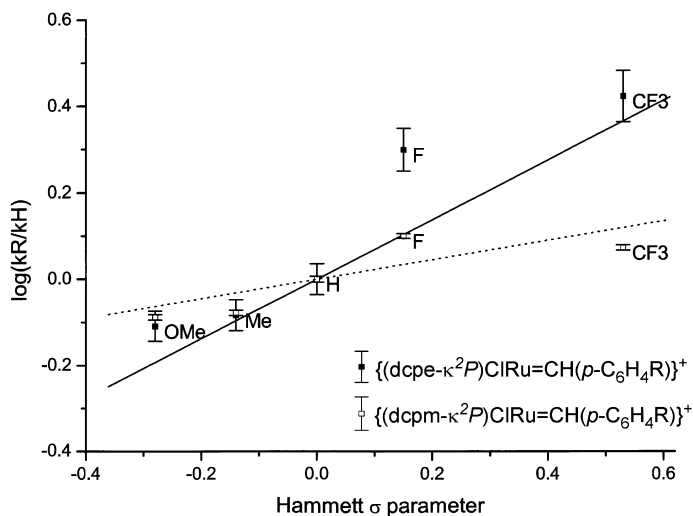


Fig. 1.10-16. Hammett plot for the relative rates of $\{[(dcpm)-\kappa^2P](Cl)Ru=CH(p-C_6H_4R)]^+\}$ (**38B–42B**, empty rectangles) and $\{[(dcpe)-\kappa^2P](Cl)Ru=CH(p-C_6H_4R)]^+\}$ (**38B–42B**, solid rectangles) with ethyl vinyl ether.

ent types of reactions (**16B** with 1-butene and norbornene and **36B** and **41B** with EVE) and is therefore unlikely to arise from uncertainties of the method.

Gas-phase secondary kinetic isotope effects for the α H atom on the benzyldiene group of **11B** were measured for the acyclic metathesis reaction from the benzyldiene complex with 1-butene to give the propylidene complex **20F** and, in the reverse direction, from **20F** to **11B**. The reactions gave inverse secondary isotope effects of $kH/kD = 0.80 \pm 0.03$ and $kH/kD = 0.86 \pm 0.07$ for both the forward and the reverse reaction [36]. The isotope effect for the reaction of **11B** with norbornene was $kH/kD = 0.96 \pm 0.04$.

For the reaction of the Hofmann-type systems **33B/33B- d_6** and **38B/38B- d_6** with ethyl vinyl ether, the secondary isotope effects were $kH/kD = 0.92 \pm 0.02$ and $kH/kD = 0.68 \pm 0.08$. The reverse of the reaction, reaction of the ethoxymethylidene complex with styrene or styrene- d_8 , was too slow to be observed within the timescale of our experiments, i.e., <10 ms.

From experiments to the surface Qualitative reaction coordinates are depicted in Figure 1.10-17. The overall topology conforms to the general picture for a bimolecular ion-molecule reaction proceeding via initial complexation [38, 39, 77–81]. The reaction coordinates were constructed with the following considerations:

- The reactions of **11B** with 1-butene and **11B** with norbornene are both exothermic, with the latter being much more exothermic than the former [82].
- The ion-dipole complex for the gas-phase reaction is assumed to correspond functionally to the π complex of the solution-phase reaction.
- While a solution-phase reaction that proceeded at less than the diffusion-controlled rate would necessarily have a rate-limiting transition state above the entering asymptote, gas-phase ion-molecule reactions with a central barrier (in the conventional double-well potential) below the reactant asymptote can proceed with less than unit reaction efficiency and display substituent and isotope effects [83]. Nevertheless, because the reaction of **11B** with 1-butene displays an extraordinarily low reaction efficiency of 10^{-4} to 10^{-5} for an exothermic ion-molecule reaction, the rate-determining transition states in the upper panels of Figure 1.10-17 have been depicted (for convenience) to lie at roughly the level of the entering asymptote. However, this is not meant to imply a quantitative assessment.
- The Hammond Postulate is assumed to be valid. Within this framework, the particular direction of the substituent effect is easily rationalized if one proceeds from the assumption that the ruthenium center in **11** is electron deficient and is accordingly destabilized by electron-withdrawing substituents on the benzyldiene fragment. The aryl group on the corresponding metallacyclobutane is, however, no longer in direct conjugation to the ruthenium. By this logic, the metallacyclobutane, and any putative transition state leading to it from a carbene complex, is destabilized less by electron withdrawal than either the carbene or the carbene/olefin π complex would be, leading to a moderately large, positive Hammett ρ value. This would necessarily make the transition state in which

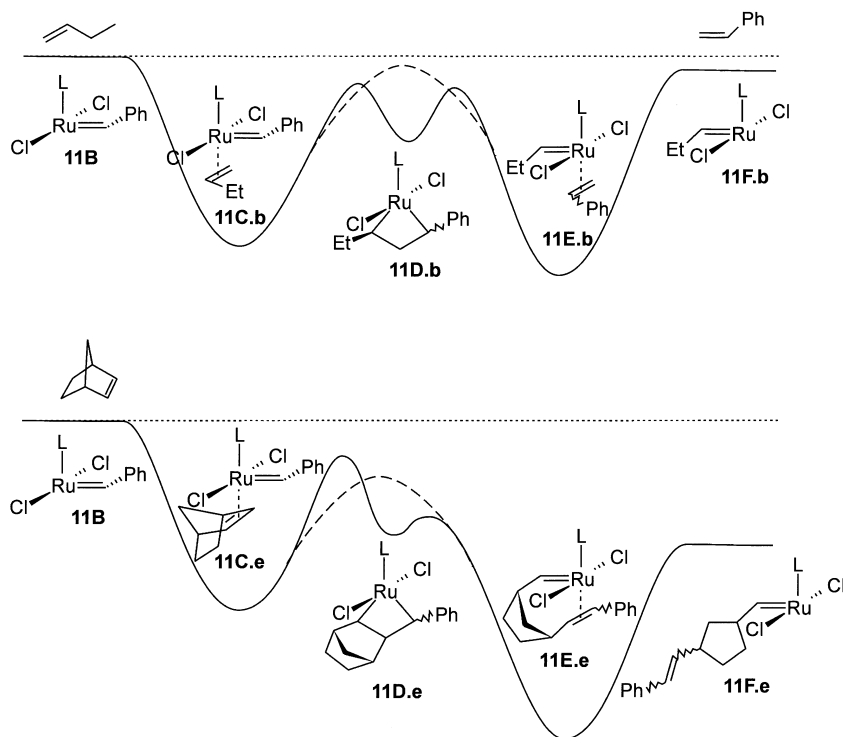


Fig. 1.10-17. Qualitative energy surface for the one-step (dashed) or two-step mechanism (solid) for the olefin metathesis of 1-butene (top) and norbornene (bottom) by **11**.

a metallacyclobutane structure is formed rate determining. Furthermore, the secondary deuterium kinetic isotope effect in the forward direction, $kH/kD = 0.80 \pm 0.03$, considered in the usual way, indicates an $sp^2 \rightarrow sp^3$ transition going to the rate-determining transition state, which is also consistent with the assignment of the rate-determining step for the gas-phase reaction of **11B** with 1-butene.

- Whether the one-step metathesis reaction (Figure 1.10-17, dashed) or the two-step metathesis reaction (Figure 1.10-17, solid) is correct is distinguished by the secondary inverse isotope effect for both the forward reaction and the backward reaction, $kH/kD = 0.86 \pm 0.07$, indicating a rate-limiting $sp^2 \rightarrow sp^3$, which is only the case in the one-step metathesis reaction (Figure 1.10-17, dashed).
- The energy surface of the reaction with norbornene is constructed according to the same principles as applied for the reaction with 1-butene. The thermochemistry going from **11B** to the first π complex **11C.e** should not be too different from that in the corresponding step in acyclic metathesis because little of the

strain in norbornene is released by π complexation [84]. Likewise, formation of the metallacyclobutane releases little strain if the metallacyclobutane is a bound intermediate (Figure 1.10-17, bottom, solid). For the one-step metathesis reaction, the metallacyclobutane is in a transition state, and by Hammond's postulate, the rate-determining transition state will be pulled down by the strain release ongoing from reactant to product (Figure 1.10-17, bottom, dashed). Whereas the inverse isotope effect in the forward direction supports a one-step mechanism as well as a two-step mechanism, the distinction can be made from the absence of an electronic effect on the reaction rate with norbornene, $\rho = -0.08 \pm 0.09$, which affords a rate-limiting step far below the energy of the level of entering asymptote. This is only the case for the one-step mechanism (Figure 1.10-17, bottom, dashed).

Refining the energy surface: computations Up to this point, the energy surface has been constructed from experiments alone. Experiments, however, cannot probe all features. While gas-phase studies can probe the reaction without interference from some of the pre-equilibria that occur in solution, other features of the potential surface, structures in particular, can be difficult to access. Computations can help in this connection. Even if the numerical accuracy is dependent on the level of theory applied, the overall topology can be obtained for comparison to experiment. The increasing set of experimental reactivity data for ruthenium-carbene complexes [15, 20, 36, 56, 61] has motivated others [16, 17] and ourselves [18] to perform a second generation of computations on ruthenium-carbene complexes after a first generation of computations [36, 85–87].

Through the course of our calculations, we have chosen the computationally less demanding QM/MM hybrid method [88, 89] in order to treat the real catalyst system instead of extrapolating the behavior of a model system to the real system. Moreover, a full exploration of the conformational space can be done. Especially the steric effects of the very large ligands (Tolman cone angles [54] for PCy_3 , PMe_3 , and PH_3 are 170° , 118° , and 87° , respectively) can be treated explicitly; these steric effects are, in fact, critical to the conclusion of this study.

The computational method was tested on the experimentally accessible electronic effects, and the energy surfaces were then refined for cyclic and acyclic substrates, giving a different topology for olefin metathesis by first- and second-generation catalysts due to a different symmetry of the ligands. An attempt to explain halogen effects will follow.

Computational evidence for LFER and isotope effects The electronic effects on the benzylidene ligands were considered as ground-state effects, where electron-withdrawing groups would destabilize the electron-poor 14-electron intermediates $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)(\text{Cl})_2\text{Ru}=\text{CH}-m,p\text{-C}_6\text{H}_4\text{R}'\}^+$ ($\text{R} = \text{H}$ (11B), OMe (12B), $t\text{-Bu}$ (13B), $p\text{-Me}$ (14B), $m\text{-Me}$ (15B), $p\text{-F}$ (16B), and $p\text{-COOMe}$ (17B)) through conjugation [36]. Table 1.10-2 lists reaction rates, experimental $\Delta G^\ddagger_{\text{exp}}$ values [90], computational $\Delta E_{\text{QM/MM}}$ values, and the Mulliken population on ruthenium of 11B–17B and 11D.a–17D.a, which can be assigned to the charge on the ruthenium center.

Tab. 1.10-2. Reaction rates for $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CH}-p\text{-C}_6\text{H}_4\text{X}$ (**11–17**) with 1-butene and QM/MM Mulliken population on Ru for **11B–17B** and **11D.a–17D.a** and the difference of their Mulliken population.

	k_{rel}	ΔG_{exp}^\ddagger (kcal mol ⁻¹)	$\Delta E_{QM/MM}$ (kcal mol ⁻¹)	B	D.a	Δq
17 (COOMe)	1.82	-0.41	-1.05	1.176	1.63	0.454
16 (F)	1.68	-0.35	-0.24	1.169	1.625	0.457
11 (H)	1.0	0	0	1.172	1.626	0.455
14 (<i>p</i> -Me)	0.8	0.15	0.3	1.172	1.628	0.456
13 (<i>t</i> -Bu)	0.85	0.11	0.11	1.172	1.632	0.460
12 (OMe)	0.6	0.35	0.55	1.170	1.631	0.461

Both the energy differences $\Delta E_{QM/MM}$ and the difference in the Mulliken population Δq of ruthenium between **B** and **D.a**, with the exception of $\text{X} = \text{F}$, correlate well with the estimated ΔG_{exp}^\ddagger values. Although the assumption that there was no electronic effect for the metallacyclobutane through the absence of conjugative effects is not strictly correct, the interpretation of the observed rate acceleration by electron-withdrawing groups is supported by the computations. The secondary isotope effects have been reproduced by computations on the model system $(\text{PH}_3)_2(\text{Cl})_2\text{Ru}=\text{CH}_2$ [36].

The rate-limiting step depends on the substrate The QM/MM energy surface for the degenerate olefin metathesis reaction of $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CH}_2$ (**7**) with ethylene (**.a**) and norbornene (**.e**) is shown in Figure 1.10-18. Comparison with the qualitative energy surfaces in Figure 1.10-17 reveals remarkable consistency: first, the assumption that the level of the entering asymptote and the subsequent steps are roughly the same and second, the energy surfaces for the reaction of **7B** with ethylene and with norbornene look essentially the same up to the metallacyclobutane (structures **A** to **D**). However, the metallacyclobutane itself – in contrast to the conclusion out of the inverse secondary isotope effects and the Hammond postulate – is found to be an intermediate (*vide infra*). The energy for the following structures **E** to **G** roughly differs by the released strain energy of norbornene (≈ 15 kcal mol⁻¹ [36, 91]), and there is no high barrier relative to the entering asymptote after metallacyclobutane formation for the reaction with norbornene. It is also important to note that dissociation and association of the phosphane ligands as well as of the olefin reactants and products are barrier-less on the ΔE surface in the case of the *trans* chlorine complexes (see also [16]), but the dissociation of the intramolecularly bound growing polymer **7E.e** \rightarrow **7F.e**, shows a significant (steric) barrier in order to achieve the open-chain conformation. The transition states **7C.a** \rightarrow **7D.a** and **7D.a** \rightarrow **7E.a** are not degenerate because of the PCy_3 ligand, which requires a rotation along reaction coordinate. Estimating a ≈ 12 kcal mol⁻¹ contribution due to the entropy for dissociative steps [16] (going to a ΔG surface), the sterically less-favorable ring opening reaction **7D** \rightarrow **7E** becomes the rate-limiting transition state for the degenerate metathesis of ethylene (a deeper

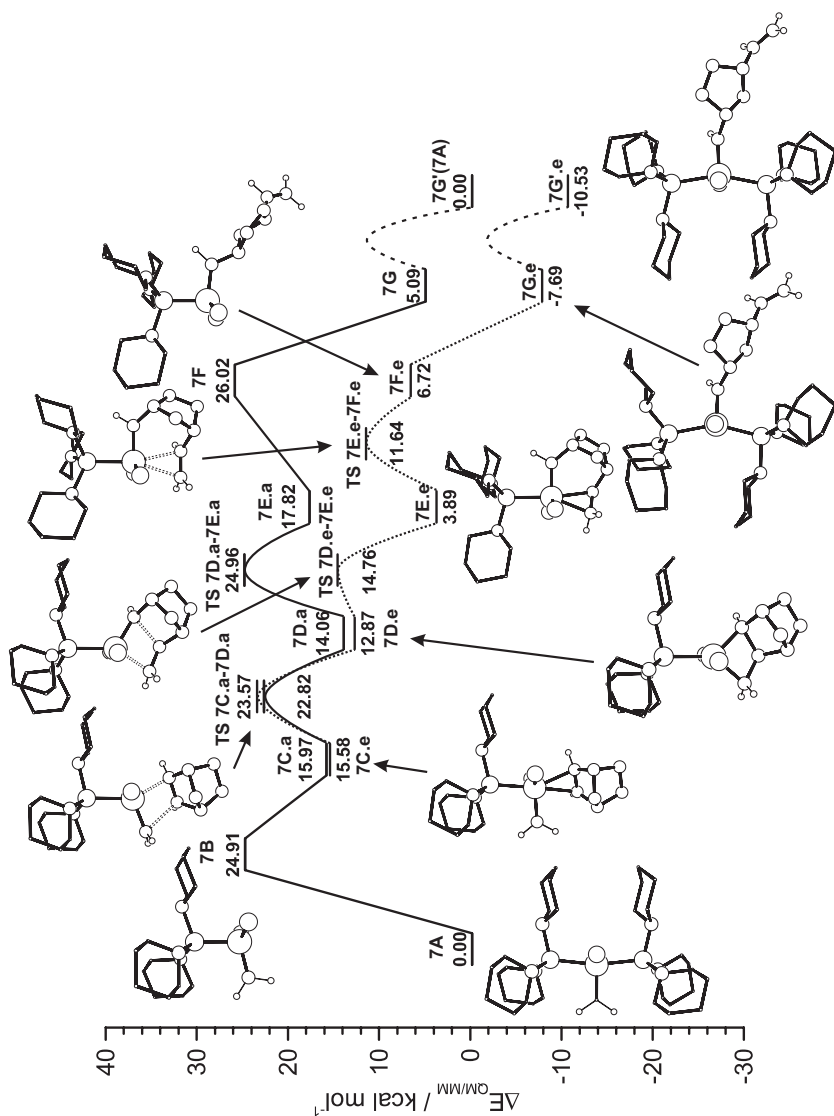


Fig. 1.10-18. Reaction coordinate for the metathesis of ethylene (solid) and norbornene (dashed) by **7** with QM/MM energies. The energy scale is in kcal mol⁻¹. Free ligands needed for mass balance are not shown but were included in the calculation. QM/MM-optimized structures for the reaction with norbornene. Balls: QM part; sticks: MM part. The structures for the reaction with ethylene **7C.a–7G.a** look apparently the same.

discussion involving the rotation of the PCy₃ ligand is presented in the following section). For norbornene, on the other hand, the ring-opening reaction **7D.e** → **7E.e** is so exothermic that **7C.e** → **7D.e** becomes the rate-limiting transition state.

The different topology of the energy surface for olefin metathesis by first- and second-generation catalysts: ligand rotation The results for the degenerate metathesis of styrene by **2** are shown in Figure 1.10-19. Grubbs reported 23.6 ± 0.5 and 27 ± 2 kcal mol⁻¹ for the enthalpies of activation for phosphine exchange from **2** and **21**, respectively [61, 15]. The computed full DFT values of 20.8 and 28.0 kcal mol⁻¹, as well as the QM/MM results, agree gratifyingly well. The reaction coordinate in Figure 1.10-19 is representative of a thermoneutral metathesis reaction by a first-generation catalyst. Rotation of the tricyclohexylphosphane in any of the structures is primarily hindered by the unfavorable steric interaction with the large chlorine atoms. The barrier for rotation of PH₃ was computed to be only 0.16 kcal mol⁻¹, illustrating the very large difference between PH₃ and PCy₃. Other studies found rotation barriers between 7 and 18 kcal mol⁻¹ for sterically large phosphanes [92–96]. For second-generation catalyst **21**, the potential surface is much simpler; a cursory examination of the structure analogous to **2D.d** shows that no rotation is needed because the NHC ligand has only twofold symmetry, as opposed to the threefold symmetry of the phosphine ligand in **2** (Figure 1.10-20). As mentioned above, the computed barrier for phosphine dissociation from **21** agrees well with experiments. The analogous structures for **21B–21D.a** for the metathesis of ethylene have computed energies (full DFT) of 28.0, 14.6, and 12.9 kcal mol⁻¹, relative to **21A**; the rest of the surface would be the mirror image in the case of a thermoneutral metathesis reaction.

One achieves agreement with experiments [36] if one presumes that the transition state for **2D.d** → **2E.d** lies, in reality, slightly higher in energy than that for **2D.d** → **2D'.d**; the two transition states differ by less than 1 kcal mol⁻¹ in the QM/MM calculation. For near-thermoneutral metathesis reactions by first-generation catalysts, the rate-determining step would then be ligand rotation at the metallacyclobutane structure. For strongly exothermic metathesis reactions, e.g., vinyl ethers, lowering of the energy of the transition state for **2D.c** → **2E.c**, but not that for **2D.c** → **2D'.c**, by strain release would allow rotation to occur at a later stage. Metallacyclobutane formation becomes rate limiting in the exothermic case; the transition state for **2C.c** → **2D.c** remains nevertheless higher than that for phosphine dissociation in the first-generation catalysts. With a higher barrier for phosphine dissociation, but a barrier for metallacyclobutane formation that is comparable to that in the first-generation systems, phosphine dissociation is always rate limiting for second-generation catalysts.

These conclusions are completely consistent with Grubbs' experimental findings in the case of vinyl ether [61, 15]. Moreover, the earlier presented gas-phase results are also consistent with the computed surfaces. Qualitatively, substituent and isotope effects were interpreted as indicating that the metallacyclobutane structure must be the rate-determining transition state. A more appropriate formulation

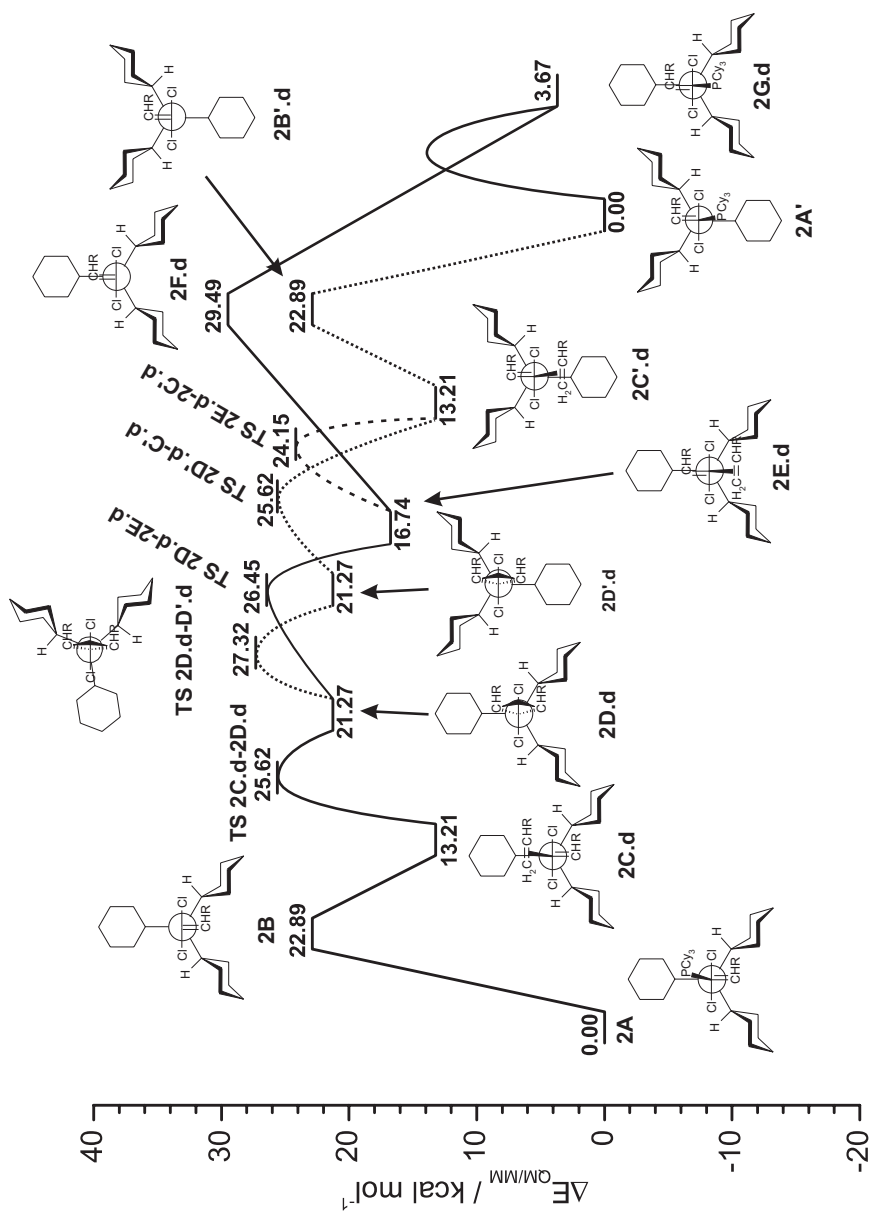


Fig. 1.10-19. Reaction coordinate for the degenerate metathesis of styrene by **2** with QM/MM energies. The energy scale is in kcal mol^{-1} . Free ligands needed for mass balance are not shown but were included in

the calculation. Complex **2** is depicted in a Newman-like projection sighting along the P–Ru bond to emphasize conformational differences.

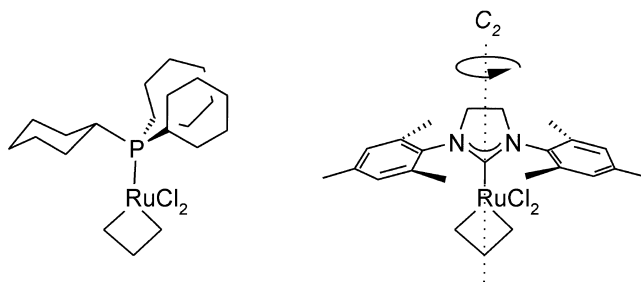


Fig. 1.10-20. Second-generation structure analogous to **D** shows that no rotation is needed because the NHC ligand has only twofold symmetry.

would be to say that the rate-determining transition state in first-generation catalysts has a metallacyclobutane structure.

While there are undoubtedly electronic effects [15–17, 61, 85, 86], especially on the precise height of the barrier for phosphine dissociation, the major topological differences between the potential surfaces for first- and second-generation metathesis catalysts can be traced to the different symmetry of the phosphine versus NHC ligands [18]. We propose that high barriers on the potential surface after the phosphine dissociation can be eliminated by choosing ligands with twofold as opposed to threefold symmetry.

Halogen effects An explanation for several “inhomogeneous” experimental results (*vide infra*) concerning halogen effects by the ruthenium metathesis catalysts $(L)_2(X)_2Ru=CHR$ is a ticklish task, but new insight into relative energies of the key intermediates by means of QM/MM computations allows one to develop a general picture. The key experimental results are as follows: (1) for the phosphane exchange rate, a 3-fold increase for the bromide **3** and a 170-fold increase for the iodide **4** compared with **2**, explained by the size of the halogens [61]; (2) a comparable (for $L = NHC$ [61]) or lower (for $L = PR_3$ [13]) reactivity in olefin metathesis for the heavier homologues; and (3) from our gas-phase results, a higher reactivity for the chloride 14-electron species **2B** and **24B** [20, 14]. For a review, see [97].

Phosphane dissociation energies for $(PCy_3)_2(X)_2Ru=CHPh$ have been computed to be 20.26 (**1**, $X = F$), 22.89 (**2**, $X = Cl$), 22.22 (**3**, $X = Br$), and 20.11 kcal mol⁻¹ (**4**, $X = I$), which agrees gratifyingly well with experimental dissociation energies of $\Delta H_{exp} = 23.6 \pm 0.5$ ($X = Cl$), 23.1 ± 0.3 ($X = Br$), and 19.0 ± 0.5 ($X = I$) kcal mol⁻¹ by Grubbs et al. [61].

Table 1.10-3 shows the relative computed energies for the degenerate olefin metathesis reaction of $(PCy_3)_2(X)_2Ru=CH_2$ (**6–9** $X = F, Cl, Br, I$) with ethylene. The transition state for the rotation of the PCy_3 ligand **TS D.a** \rightarrow **D'.a** can easily be accessed through its $C(s)$ symmetric nature. The energy profile for two alternative reaction coordinates is shown in Figure 1.10-21: (1) a pathway without rotation of the PCy_3 ligand **B** \rightarrow **C.a** \rightarrow **D.a** \rightarrow **E.a** \rightarrow **F.a** and (2) a pathway with ligand rota-

Tab. 1.10-3. Relative QM/MM energies $\Delta E_{\text{QM/MM}}$ for the reaction of $(\text{PCy}_3)_2(\text{X})_2\text{Ru}=\text{CH}_2$ (**6–9**) with ethylene in kcal mol⁻¹. The 14-electron species **B** are assumed as reference structures at zero energy.

	6 (F)	7 (Cl)	8 (Br)	9 (I)
	$\Delta E_{\text{QM/MM}}$	$\Delta E_{\text{QM/MM}}$	$\Delta E_{\text{QM/MM}}$	$\Delta E_{\text{QM/MM}}$
A	-25.31	-24.91	-23.87	-22.87
B	0.00	0.00	0.00	0.00
C	-10.94	-8.94	-8.49	-8.06
D	-5.84	-10.85	-10.84	-10.02
E	-10.81	-7.09	-6.01	-4.8
F	0.16	1.11	1.43	1.39
G	-10.58	-16.58	-15.68	-14.25
TS D-D'	-2.08	-5.75	-5.15	-4.01

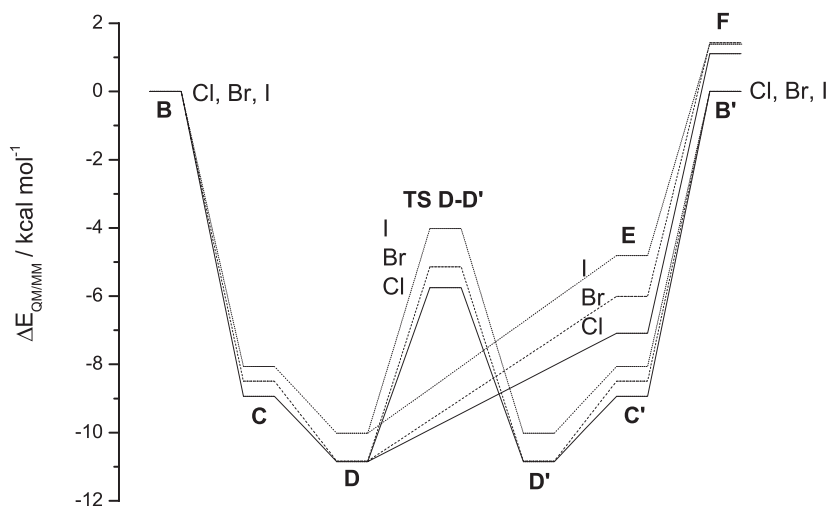


Fig. 1.10-21. QM/MM energy profile for the reaction of $(\text{PCy}_3)_2(\text{X})_2\text{Ru}=\text{CH}_2$ (**6–9** X = F, Cl, Br, I) with ethylene. The 14-electron active species **B** are assumed as reference structures at zero energy.

tion **B** → **C.a** → **D.a** → **D'.a** → **C'.a** → **B'** (see also Figure 1.10-19). As outlined before, a reaction pathway without rotation of the PCy_3 ligand (pathway 1) would lead to a 14-electron species **F.a** that has to be higher in energy than the corresponding 14-electron complex **B** due to unfavorable steric interaction of the PCy_3 ligand with the carbene C atom and therefore – in the case of a thermoneutral olefin metathesis reaction – the symmetric reaction pathway (pathway 2), which requires rotation of the PCy_3 ligand, is favored.

The sole reaction step that would significantly depend on the steric difference of chlorine versus iodine is the rotation for the PCy_3 ligand, where two β -hydrogen atoms of the cyclohexyl residue are within van der Waals distance with one halide.

Consequently, the transition state for the ligand rotation (**TS D.a** \rightarrow **D'.a**) in Figure 1.10-21 is significantly higher in energy for the diiodide than for the dichloride. After rotation, metallacyclobutane ring opening, and release of the olefin, the equienergetic 14-electron complex **B'** is formed.

The computed relative activation energies for reaction pathway 2 are -5.75 (Cl), -5.15 (Br), and -4.01 (I) kcal mol $^{-1}$, and through this means the relative gas-phase rates $\text{Cl}_2 > \text{ClI} \gg \text{I}_2$ are explained. The overall solution-phase activation energies for reaction pathway 2 are 19.16 (Cl), 18.72 (Br), and 18.86 (I) kcal mol $^{-1}$. This would mean a relative solution-phase reactivity of $\text{Br}_2 \approx \text{I}_2 \geq \text{Cl}_2$, which still does not quite agree with solution-phase reactivities [13].

The reaction coordinate for second-generation ruthenium complexes, on the other hand, does not require a sterically demanding ligand rotation, and therefore the diiodide should react faster than the dichloride complex due to facilitated phosphane dissociation as is the case in solution-phase experiments for **21** with COD [61]. This prediction remains to be tested.

1.10.5

Conclusions

Gas-phase investigations of ruthenium carbene complexes known to perform the same reaction in solution have been demonstrated to be reliable in terms of predicting their solution-phase behavior. Not only are they suited to screen a large set of different ligands with relatively small effort, but also much mechanistic information can be drawn from the capability of gas-phase chemistry to directly study the active species without any preceding dissociation step.

We find that this preceding dissociation step can in fact influence the overall catalyst rate more than the intrinsic reactivity of the active species itself by a higher fraction of activated catalyst present in solution as for the $\{[\text{R}_2\text{P}(\text{CH}_2)_n\text{PR}_2-\kappa^2\text{P}](\text{X})\text{Ru}=\text{CHR}'\}_2^{2+}$ systems. Secondly, for acyclic metathesis, enhanced π -complex formation increases the rate, whereas the same phenomenon decreases overall rate in ROMP, as has been shown for different $\{[\text{R}_2\text{P}(\text{CH}_2)_n\text{PR}_2-\kappa^2\text{P}](\text{X})\text{Ru}=\text{CHR}'\}^+$ systems as well as for first- and second-generation ruthenium-carbene complexes. First- and second-generation ruthenium-carbene complexes also distinguish in their catalyst commitment; while there is a significant barrier in olefin metathesis for the first-generation catalysts after formation of the active 14-electron species, these barriers are similar or even lower in energy than the 14-electron species for second-generation catalysts. Whereas a part of this difference is electronic, the mismatched threefold symmetry of the PCy_3 ligand adds a further steric contribution.

Compound Numbers

- 1 $(\text{PCy}_3)_2(\text{F})_2\text{Ru}=\text{CHPh}$
- 2 $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}$

- 3 $(\text{PCy}_3)_2(\text{Br})_2\text{Ru}=\text{CHPh}$
- 4 $(\text{PCy}_3)_2(\text{I})_2\text{Ru}=\text{CHPh}$
- 5 $\{(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHC}_6\text{H}_4\text{CH}_2\text{N}(\text{CH}_3)_3\}^+$
- 6 $(\text{PCy}_3)_2(\text{F})_2\text{Ru}=\text{CH}_2$
- 7 $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CH}_2$
- 8 $(\text{PCy}_3)_2(\text{Br})_2\text{Ru}=\text{CH}_2$
- 9 $(\text{PCy}_3)_2(\text{I})_2\text{Ru}=\text{CH}_2$
- 10 $\{(\text{PCy}_3)_2(\text{Cl})\text{Ru}=\text{CHPh}\}^+$
- 11 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CHPh}\}^{2+}$
- 12 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{OMe}\}^{2+}$
- 13 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{-}t\text{-Bu}\}^{2+}$
- 14 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{Me}\}^{2+}$
- 15 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CH-}m\text{-C}_6\text{H}_4\text{Me}\}^{2+}$
- 16 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{F}\}^{2+}$
- 17 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{COOMe}\}^{2+}$
- 18 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})(\text{I})\text{Ru}=\text{CHPh}\}^{2+}$
- 19 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{I})_2\text{Ru}=\text{CHPh}\}^{2+}$
- 20 $\{(\text{PCy}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_3)_2(\text{Cl})_2\text{Ru}=\text{CHEt}\}^{2+}$
- 21 $(_2\text{IMes})(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$
- 22 $(_2\text{IMes})(\text{PCy}_3)(\text{Cl}_2)\text{RuCl}_2=\text{CH}_2$
- 23 $\{(_2\text{IMes})(\text{PCy}_3)(\text{Cl}_2)\text{Ru}=\text{CHC}_6\text{H}_4\text{CH}_2\text{N}(\text{CH}_3)_3\}^+$
- 24 $\{[(\text{dtbpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)_2\}_2^{2+}$
- 25 $\{[(\text{dtbpm})-\kappa^2\text{P}](\text{Br})\text{Ru}=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)_2\}_2^{2+}$
- 26 $\{[(\text{dtbpm})-\kappa^2\text{P}](\text{I})\text{Ru}=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)_2\}_2^{2+}$
- 27 $\{[(\text{dtbpm})-\kappa^2\text{P}](\text{OTf})\text{Ru}=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)_2\}_2^{2+}$
- 28 $\{[(\text{dtbpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CHCH}(\text{CH}_3)_2\}_2^{2+}$
- 29 $\{[(\text{dtbpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CHPh}\}_2^{2+}$
- 30 $\{[(\text{dtdpm})_2-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH}_2\}_2^{2+}$
- 31 $\{[(\text{dtbpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)_2\}_2^{2+}$
- 32 $\{[(\text{dtbpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CHPh}\}_2^{2+}$
- 33 $\{[(\text{dcpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CHPh}\}_2^{2+}$
- 34 $\{[(\text{dcpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{OMe}\}_2^{2+}$
- 35 $\{[(\text{dcpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{Me}\}_2^{2+}$
- 36 $\{[(\text{dcpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{F}\}_2^{2+}$
- 37 $\{[(\text{dcpm})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{CF}_3\}_2^{2+}$
- 38 $\{[(\text{dcpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CHPh}\}_2^{2+}$
- 39 $\{[(\text{dcpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{OMe}\}_2^{2+}$
- 40 $\{[(\text{dcpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{Me}\}_2^{2+}$
- 41 $\{[(\text{dcpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{F}\}_2^{2+}$
- 42 $\{[(\text{dcpe})-\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH-}p\text{-C}_6\text{H}_4\text{CF}_3\}_2^{2+}$
- 43 $\{\text{Solv-}(\text{PCy}_3)_2(\text{Cl})(\text{H})\text{Ru}\equiv\text{CPh}\}^+$
- 44 4-[(Z)-2-pentenyl-3,4,4,5,5,5- d_6]-cyclopentene
- 45 4-[(Z)-2-pentenyl-3,4,4,5,5,5- d_6]-cyclopentene
- 46 $\text{C}_7\text{H}_9\text{CH}_2\text{PPh}_3^+$
- 47 ringclosing products

References

- 1 KATZ, T. J.; STEVEN, J. L.; ACTON, N. *Tet. Lett.* **1976**, 17, 4247–4250.
- 2 SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DiMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, 112, 3875–3886.
- 3 SCHROCK, R. R. *Acc. Chem. Res.* **1990**, 23, 158–165.
- 4 NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1992**, 114, 3974–3975.
- 5 HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSEN, J. L. *J. Am. Chem. Soc.* **1999**, 121, 2674–2678.
- 6 WESKAMP, T.; SCHATTEMMANN, W. C.; SPIEGLER, M.; HERRMANN, W. A. *Ang. Chem., Int. Ed.* **1998**, 37, 2490–2493; HERRMANN, W. A. *Corrigendum: Ang. Chem., Int. Ed.* **1999**, 38, 262.
- 7 SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 953–956.
- 8 MOHR, B.; LYNN, D. M.; GRUBBS, R. H. *Organometallics* **1996**, 15, 4317–4325.
- 9 STUER, W.; WOLF, J.; WERNER, H.; SCHWAB, P.; SCHULZ, M. *Ang. Chem., Int. Ed.* **1998**, 37, 3421–3423.
- 10 HANSEN, S. M.; VOLLAND, M. A. O.; ROMINGER, F.; EISENTRAGER, F.; HOFMANN, P. *Ang. Chem., Int. Ed.* **1999**, 38, 1273–1276.
- 11 FÜRSTNER, A.; PICQUET, M.; BRUNEAU, C.; DIXNEUF, P. H. *Chem. Commun.* **1998**, 1315–1316.
- 12 PICQUET, M.; BRUNEAU, C.; DIXNEUF, P. H. *Chem. Commun.* **1998**, 2249–2250.
- 13 DIAS, E. L.; NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1997**, 119, 3887–3897.
- 14 HINDERLING, C.; ADLHART, C.; CHEN, P. *Ang. Chem., Int. Ed.* **1998**, 37, 2685–2689.
- 15 SANFORD, M. S.; ULMAN, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, 123, 749–750.
- 16 VYBOISHCHIKOV, S. F.; BÜHL, M.; THIEL, W. *Chem. Eur. J.* **2002**, 8, 3962–3974.
- 17 CAVALLO, L. *J. Am. Chem. Soc.* **2002**, 124, 8965–8973.
- 18 ADLHART, C.; CHEN, P. *Angw. Chem., Int. Ed.* **2002**, 41, 4484–4487.
- 19 HANSEN, S. M.; ROMINGER, F.; METZ, M.; HOFMANN, P. *Chemistry – A European Journal* **1999**, 5, 557–566.
- 20 VOLLAND, M. A. O.; ADLHART, C.; KIENER, C. A.; CHEN, P.; HOFMANN, P. *Chem. Eur. J.* **2001**, 7, 4621–4632.
- 21 COLE, R. B. *Electrospray Ionization Mass Spectrometry*; John Wiley, New York: USA, 1997.
- 22 HENDERSON, W.; NICHOLSON, B. K.; MCCAFFREY, L. J. *Polyhedron* **1998**, 17, 4291–4313.
- 23 CHEN, P. *Angw. Chem., Int. Ed.* **2003**, 42, 2–17.
- 24 DOLE, M.; HINES, R. L.; MACK, R. C.; MOBLEY, R. C.; FERGUSON, L. D.; ALICE, M. J. *Chem. Phys.* **1968**, 49, 2240–2249.
- 25 YAMASHITA, M.; FENN, J. B. *J. Phys. Chem.* **1984**, 88, 4451–4459.
- 26 YAMASHITA, M.; FENN, J. B. *J. Phys. Chem.* **1984**, 88, 4671–4675.
- 27 FENN, J. B.; MANN, M.; MENG, C. K.; WONG, S. F.; WHITEHOUSE, C. M. *Science* **1989**, 246, 64–71.
- 28 SIUZDAK, G.; BOTHNER, B.; YEAGER, M.; BRUGIDOU, C.; FAUGE, C. M.; HOEY, K.; CHANG, C.-M. *Chem. Biol* **1996**, 3, 45–48.
- 29 SCHMEIZER-REDEKER, G.; BÜTTERLING, L.; RÖLLGEN, F. W. *Int. J. Mass Spectrom. Ion Proc.* **1989**, 90, 139–150.
- 30 IRIBARNE, J. V.; THOMSON, B. A. *J. Chem. Phys.* **1976**, 64, 2287–2294.
- 31 THOMSON, B. A.; IRIBARNE, J. V. *J. Chem. Phys.* **1979**, 71, 4451–4463.
- 32 KEBARLE, P.; TANG, L. *Anal. Chem.* **1993**, 65, 972A–986A.
- 33 FENN, J. B. *J. Am. Soc. Mass Spectrometry* **1993**, 4, 524–535.
- 34 LANGEVIN, P. M. *Ann. Chim., Phys.* **1905**, 5, 245.
- 35 SU, T.; BOWERS, M. T.; ANICICH, V. C. *J. Chem. Phys.* **1973**, 58, 5175–5176.
- 36 ADLHART, C.; HINDERLING, C.; BAUMANN, H.; CHEN, P. *J. Am. Chem. Soc.* **2000**, 122, 8204–8214.
- 37 BOWERS, M. T. *Gas Phase Ion Chemistry*, 3 vols.; Academic Press: New York, 1979–1984.

- 38 FARNETH, W. E.; BRAUMAN, J. I. *J. Am. Chem. Soc.* **1976**, 98, 7891–7898.
- 39 SHARMA, D. K. S.; KEBARLE, P. J. *Am. Chem. Soc.* **1982**, 104, 19–24.
- 40 BOHME, D. K.; MACKEY, G. I. *J. Am. Chem. Soc.* **1981**, 103, 978–979.
- 41 HINDERLING, C.; PLATTNER, D. A.; CHEN, P. *Ang. Chem., Int. Ed.* **1997**, 36, 243–244.
- 42 HINDERLING, C.; FEICHTINGER, D.; PLATTNER, D. A.; CHEN, P. *J. Am. Chem. Soc.* **1997**, 119, 10793–10804.
- 43 STEVENS, A. E.; BEAUCHAMP, J. L. *J. Am. Chem. Soc.* **1979**, 101, 6449–6450.
- 44 JACOBSON, D. B.; FREISER, B. S. *J. Am. Chem. Soc.* **1985**, 107, 67–72.
- 45 JACOBSON, D. B.; FREISER, B. S. *J. Am. Chem. Soc.* **1985**, 107, 2605–2612.
- 46 LIN, P.; KENTTAMAA, H. I. *Chem. Rev.* **1992**, 92, 1649–1665.
- 47 SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, 118, 100–110.
- 48 WU, Z.; NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1995**, 117, 5503–5511.
- 49 WU, Z.; BENEDICTO, A. D.; GRUBBS, R. H. *Macromolecules* **1993**, 26, 4975–4977.
- 50 PATTON, P. A.; MCCARTHY, T. J. *Macromolecules* **1984**, 17, 2939–2940.
- 51 PATTON, P. A.; MCCARTHY, T. J. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1985**, 26, 66–67.
- 52 PATTON, P. A.; MCCARTHY, T. J. *Macromolecules* **1987**, 20, 778–782.
- 53 VOLLAND, M. A. O. Doktorarbeit, Universität Heidelberg, 2001.
- 54 TOLMAN, C. A. *Chem. Rev.* **1977**, 77, 313–348.
- 55 HOFMANN, P.; VOLLAND, M. A. O.; HANSEN, S. M.; EISENTRAGER, F.; GROSS, J. H.; STENGEL, K. J. *Organomet. Chem.* **2000**, 606, 88–92.
- 56 ADLHART, C.; VOLLAND, M. A. O.; HOFMANN, P.; CHEN, P. *Helv. Chim. Acta* **2000**, 83, 3306–3311.
- 57 GONZÁLEZ-HERRERO, P.; WEBERNDÖRFER, B.; ILG, K.; WOLF, J.; WERNER, H. *Angw. Chem., Int. Ed.* **2000**, 39, 3266–3269.
- 58 GONZÁLEZ-HERRERO, P.; WEBERNDÖRFER, B.; ILG, K.; WOLF, J.; WERNER, H. *Organometallics* **2001**, 20, 3672–3685.
- 59 LYNN, D. M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, 123, 3187–3193.
- 60 LYNN, D. M.; MOHR, B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1998**, 120, 1627–1628.
- 61 SANFORD, M. S.; LOVE, J. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, 123, 6543–6554.
- 62 BIELAWSKI, C. B.; GRUBBS, R. H. *Angw. Chem., Int. Ed.* **2000**, 39, 2903–2906.
- 63 Crossover experiments with $\{[(t\text{-Bu})_2\text{P}(\text{CH}_2)\text{P}(t\text{-Bu})_2\text{-}\kappa^2\text{P}](\text{Cl})\text{Ru}=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)_2\}^+$ [20] as well as calculations support the attribution of the π complex.
- 64 TALLARICO, J. A.; BONITATEBUS, PETER, J. J.; SNAPPER, M. L. *J. Am. Chem. Soc.* **1997**, 119, 7157–7158.
- 65 TOLEDANO, A. C.; RUDLER, H.; DARAN, J.-C.; JEANNIN, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 9, 574–576.
- 66 TOLEDANO, A. C.; PARLIER, A.; RUDLER, H.; DARAN, J. C.; JEANNIN, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 9, 576–578.
- 67 Computational details: ADF 2000.02 code [98] with IMOMM [88, 89] implementation; with H dummy atoms with H dummy atoms ($\alpha_1 = 1.3971$). I: triple- ζ (Type IV), $s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^2 4p^6$ electrons frozen; Ru: triple- ζ (Type IV), $s^2 2s^2 2p^6 3s^2 3p^6 3d^{10}$ electrons frozen; Br: double- ζ (Type III), $1s^2 2s^2 2p^6 s^2 3p^6$ electrons frozen; Cl, P: double- ζ (Type III), $1s^2 2s^2 2p^6$ electrons frozen; F, C: double- ζ (Type III), $1s^2$ electrons frozen; H: double- ζ (Type III); BP86 [99, 100] with LDA [101]. Scalar relativistic corrections. For the MM part of the calculation, a modified sybyl/tripos 5.2 force field [102] for Ru was used [18].
- 68 Syndiotactic and isotactic living polymers have been calculated according to the fact, that fgfstm preferably polymerizes norbornene (ROMP) in an isotactic way [103], whereas for ROMP with fgndm syndiotactic polymers are obtained [104].
- 69 PERRIN, L.; CLOT, E.; EISENSTEIN, O.; LOCH, J.; CRABTREE, R. H. *Inorg. Chem.* **2001**, 40, 5806–5811.

- 70 COLLMAN, J. P.; HEGEDUS, L. S. *Principles and Application of Organotransition Metal Chemistry*; University Science Books: Mill Valley, California, USA, 1980.
- 71 HALPERN, J. *Science (Washington, D.C., 1883-)* **1982**, 217, 401–407.
- 72 ADLHART, C.; P, C. *Helv. Chim. Acta* **2000**, 83, 2192–2196.
- 73 LEHMAN JR., S. E.; WAGENER, K. B. *Macromolecules* **2002**, 35, 48–53.
- 74 BIELAWSKI, C. B.; GRUBBS, R. H. *Macromolecules* **2001**, 34, 8838–8840.
- 75 MARCH, J. *Advanced Organic Chemistry*; John Wiley & Sons, New York: USA, 1992 Most of the electrophile additions on norbornene appear on the *exo* face.
- 76 BASU, K.; CABRAL, J. A.; PAQUETTE, L. A. *Tet. Lett.* **2002**, 43, 5453–5456.
- 77 OLMSTEAD, W. N.; BRAUMAN, J. I. *J. Am. Chem. Soc.* **1977**, 99, 4219–4228.
- 78 ASUBIOJO, O. I.; BRAUMAN, J. I. *J. Am. Chem. Soc.* **1979**, 101, 3715–3724.
- 79 PELLERITE, M. J.; BRAUMAN, J. I. *J. Am. Chem. Soc.* **1980**, 102, 5993–5999.
- 80 CALDWELL, G.; MAGNERA, T. F.; KEBARLE, P. *J. Am. Chem. Soc.* **1984**, 106, 959–966.
- 81 MCMAHON, T. B.; HEINIS, T.; NICOL, G.; HOVEY, J. K.; KEBARLE, P. *J. Am. Chem. Soc.* **1988**, 110, 7591–7598.
- 82 We expect the gas-phase reaction of **11B** with 1-butene to be mildly exothermic because, as Grubbs noted [47, 105], an alkyl group is both smaller and more electron-donating than a phenyl and, accordingly, should stabilize the ruthenium center. Relative QM/MM energies for the alkylidene complexes $(\text{PCy}_3)_2(\text{Cl})_2\text{Ru}=\text{CHR}$ in contrast are 0.00 ($\text{R} = \text{H}$, methylene), –0.26 ($\text{R} = \text{Me}$, ethylidene), 0.87 ($\text{R} = \text{Et}$, propylidene), and –1.57 ($\text{R} = \text{Ph}$, benzyldiene) kcal/mol. The ring-opening metathesis of norbornene, **11B** with norbornene, should be much more exothermic because, in addition to the electronic and steric factors, the strain release upon cleavage of the olefinic linkage in norbornene should add approximately 15 kcal/mol to the reaction exothermicity [91, 36].
- 83 JASINSKI, J. M.; BRAUMAN, J. I. *J. Am. Chem. Soc.* **1980**, 102, 2906–2913.
- 84 IVIN, K. J.; LAPIENIS, G.; ROONEY, J. J. *Makromol. Chem.* **1982**, 183, 9–28.
- 85 AAGAARD, O. M.; MEIER, R. J.; BUDA, F. *J. Am. Chem. Soc.* **1998**, 120, 7174–7182.
- 86 MEIER, R. J.; AAGAARD, O. M.; BUDA, F. *J. Mol. Cat. A Chem.* **2000**, 160, 189–197.
- 87 VOLLAND, M. A. O.; HANSEN, S. M.; HOFMANN, P. in *Chemistry at the Beginning of the Third Millennium: Molecular Design, Supramolecules, Nanotechnology and Beyond*; FABBRIZZI, L.; POGGI, A., Eds.; Springer, Berlin: Germany, 2000.
- 88 MASERAS, F.; MOROKUMA, K. J. *Comput. Chem.* **1995**, 16, 1170–1179.
- 89 WOO, T. K.; CAVALLO, T. L.; ZIEGLER, T. *Theor. Chem. Acc.* **1998**, 100, 307–313.
- 90 According to $\Delta G^\ddagger_{\text{exp}} = RT \ln k_{\text{rel}}$ at 343 K. This can only serve as an estimate.
- 91 LEBEDEV, B. V.; SMIRNOVA, N.; KIPARISOVA, E.; MAKOVETSKII, K. *Makromolekulare Chemie* **1992**, 193, 1399–1411.
- 92 ALBERT, J.; BOSQUE, R.; CADENA, J. M.; DELGADO, S.; GRANELL, J. J. *Organomet. Chem.* **634**, 83–89.
- 93 FANIZZI, F. P.; LANFRANCHI, M.; NATIEL, G.; TIRIPICCHIO, A. *Inorg. Chem.* **1994**, 33, 3331–3339.
- 94 POLOWIN, J.; BAIRD, M. C. J. *Organomet. Chem.* **1994**, 478, 45–48.
- 95 FALLER, J. W.; JOHNSON, B. V. J. *Organomet. Chem.* **1975**, 96, 99–113.
- 96 JONES, W. D.; FEHER, F. J. *Inorg. Chem.* **1984**, 23, 2376–2388.
- 97 FAGNOU, K.; LAUTENS, M. *Angew. Chem. Int. Ed.* **2002**, 41, 26–47.
- 98 VELDE, G. T.; BICKELHAUPT, F. M.; BAERENDS, E. J.; GUERRA, C. F.; VAN GISBERGEN, S. J. A.; SNIJDERS, J. G.; ZIEGLER, T. J. *Comput. Chem.* **2001**, 22, 931–967.
- 99 BECKE, A. D. *Physical Review A* **1988**, 38, 3098–3100.
- 100 PERDEW, J. P. *Physical Review B* **1986**, 33, 8822–8824.
- 101 VOSKO, S. H.; WILK, L.; NUSAIR, M. *Canad. J. Phys.* **1980**, 58, 1200–1211.

- 102 CLARK, M.; CRAMER III, R. D.; VAN OPDENBOSCH, N. J. *Comput. Chem.* **1989**, *10*, 982–1012.
- 103 AMIR-EBRAHIMI, V.; CORRY, D. A.; HAMILTON, J. G.; M., T. J.; ROONEY, J. J. *Macromolecules* **2000**, *33*, 717–724.
- 104 HAMILTON, J.; FRENZEL, U.; KOHL, F.; WESKAMP, T.; ROONEY, J.; HERRMANN, W.; NUYKEN, O. J. *Organomet. Chem.* **2000**, *606*, 8–12.
- 105 ULMAN, M.; GRUBBS, R. H. *Organometallics* **1998**, *17*, 2484–2489.

1.11

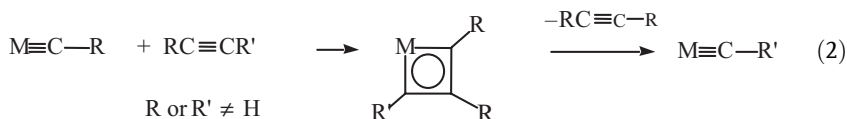
The Discovery and Development of High Oxidation State Alkylidyne Complexes for Alkyne Metathesis

Richard R. Schrock

1.11.1

Introduction

The earliest reports of alkyne metathesis (Eq. (1)) involved heterogeneous catalysts prepared from tungsten oxides on a support such as silica at 400 °C [1, 2]. Homogeneous catalysts prepared from molybdenum hexacarbonyl and a phenol followed a few years later [3–5]. In all cases the reaction was slow and the active species and mechanism were not known. In a paper concerning primarily the mechanism of alkene metathesis, Katz [6] suggested a mechanism for the alkyne metathesis reaction that was analogous to that proposed for alkene metathesis [7], namely, a reaction between a metal-carbon triple bond and an alkyne to give an intermediate metallacyclobutadiene complex (Eq. (2)). However, alkylidyne complexes that were known at that time, namely, those prepared by Fischer [8–10] (e.g., $\text{Br}(\text{CO})_4\text{W}\equiv\text{CPh}$), did not react with alkynes in a metathesis-like fashion.



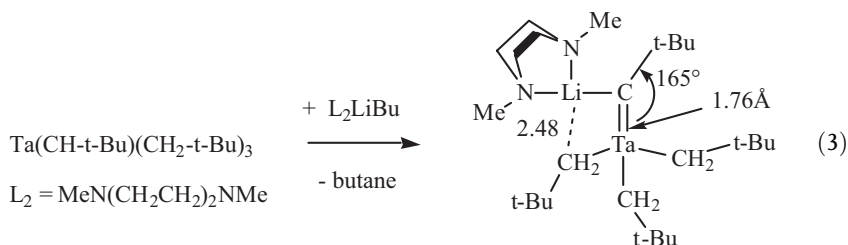
During the pursuit of well-defined catalysts for alkene metathesis [11], “high oxidation state” carbyne or alkylidyne complexes of tungsten were discovered that turned out to metathesize alkynes with remarkable ease. Although this chemistry was not pursued by organic chemists for some time, interest in the last decade in well-characterized alkene metathesis catalysts for organic reactions sparked a renewed interest in alkyne metathesis. (See other chapters in this volume.) In this chapter I trace the discovery and development of high oxidation state alkylidyne complexes that will metathesize alkynes [12]. This chemistry is closely linked to the discovery and development of high oxidation state imido alkylidene complexes for alkene metathesis discussed in another chapter in this volume. Comprehensive

reviews on high oxidation state alkylidyne complexes are available [13, 14]. This account will be more historical in nature and will concern primarily the discovery and development of alkylidyne complexes that will actually metathesize alkynes.

1.11.2

Alkylidyne Complexes of Tantalum

The first “high oxidation state” alkylidyne complex to be prepared is that shown in Eq. (3) [15]. (If an alkylidyne is regarded as a trianionic ligand, then the metal is in its highest possible oxidation state.) Although lithium was found to interact with the α carbon atom in an



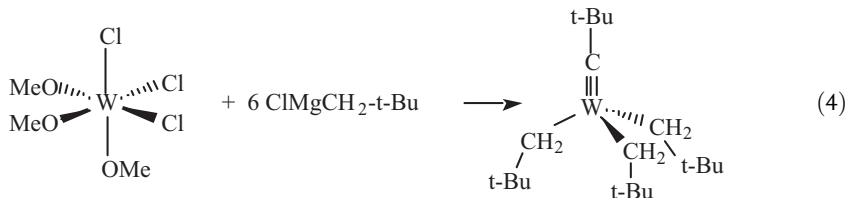
X-ray study of $[\text{Li}\{\text{MeN}(\text{CH}_2\text{CH}_2)_2\text{NMe}\}][\text{Ta}(\text{C-t-Bu})(\text{CH}_2\text{-t-Bu})_3]$ ($\text{Li-C} = 2.19(3) \text{ \AA}$), an anionic alkylidyne interpretation is more appropriate than a “lithium-substituted alkylidene” interpretation on the basis of a $\text{Ta}\equiv\text{C}$ bond distance of $1.76(2) \text{ \AA}$ and a $\text{Ta-C}_x\text{-C}_\beta$ angle of 165° . The reaction in Eq. (3) emphasized that an alkylidene proton in a high oxidation state alkylidene complex could be removed by a strong base. Soon thereafter, neutral tantalum alkylidyne complexes were prepared via intramolecular α hydrogen abstraction reactions [16]. For example, $\text{Ta}(\eta^5\text{-C}_5\text{Me}_5)(\text{CHPh})(\text{CH}_2\text{Ph})\text{Cl}$ reacts with excess trimethylphosphine to give $\text{Ta}(\eta^5\text{-C}_5\text{Me}_5)(\text{CPh})(\text{PMe}_3)_2\text{Cl}$, in which the ligands adopt a four-legged piano stool arrangement about the metal and the $\text{Ta}\equiv\text{C}$ bond distance is $1.840(8) \text{ \AA}$ [17]. Neopentylidene complexes of tantalum also could be converted into neopentylidyne hydride complexes upon reduction of the neopentylidene complex by two electrons [18]. No reactions between these early tantalum alkylidyne complexes and alkynes were explored.

1.11.3

Alkylidyne Complexes of Tungsten

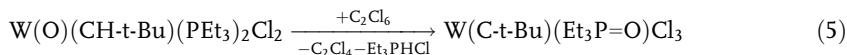
The synthesis of $(\text{Me}_3\text{CCH}_2)_3\text{Ta}=\text{CHCMe}_3$ by treating $\text{Ta}(\text{CH}_2\text{CMe}_3)_3\text{Cl}_2$ with 2 equivalents of $\text{LiCH}_2\text{CMe}_3$ in pentane [19] raised the question concerning reactions between tungsten or molybdenum chlorides and neopentyl reagents. In 1978 it was reported that reactions between neopentyllithium and WCl_6 or MoCl_5 , “re-

ducing" conditions analogous to those employed to prepare olefin metathesis catalysts *in situ* [20], gave compounds with the formula $(\text{Me}_3\text{CCH}_2)_3\text{M}\equiv\text{CCMe}_3$ in low yields (25% for $\text{M} = \text{W}$ and 15% for $\text{M} = \text{Mo}$) [12, 14, 21]. A higher yield (55%) and reliable route to the tungsten complex that was developed later is shown in Eq. (4). $(\text{Me}_3\text{CCH}_2)_3\text{W}\equiv\text{CCMe}_3$ is a volatile, yellow, crystalline compound that



melts at approximately 70 °C and can be distilled *in vacuo*, properties that are reminiscent of $(\text{Me}_3\text{CCH}_2)_3\text{Ta}=\text{CHCMe}_3$. The mechanism of forming $\text{W}(\text{C-t-Bu})(\text{CH}_2\text{-t-Bu})_3$ is believed to involve conversion of a neopentylidene ligand into a neopentylidene ligand by an α hydrogen abstraction reaction at some stage, followed by conversion of the neopentylidene ligand into a neopentylidyne ligand in a second α hydrogen abstraction step. Replacement of any remaining chloride or methoxide with a neopentyl group then completes the transformation. In view of recent studies in which the loss of hydrogen from an alkyl group in $\text{W}(\text{IV})$ triamido/amine complexes to give alkylidyne complexes has been documented [22], formation of the alkylidyne in $\text{W}(\text{C-t-Bu})(\text{CH}_2\text{-t-Bu})_3$, at least in part, by " α,α -dehydrogenation" in a $\text{W}(\text{IV})$ neopentyl intermediate cannot be entirely discounted.

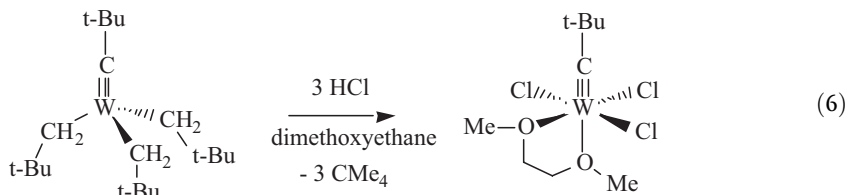
An attempt to remove a phosphine ligand in $\text{W}(\text{O})(\text{CH}_2)(\text{PEt}_3)_2\text{Cl}_2$ by oxidizing it with hexachloroethane in THF yielded the neopentylidyne complex shown in Eq. (5) [23]. It



was proposed that PEt_3Cl_2 actually does form and that $[\text{PEt}_3\text{Cl}]^+$ subsequently attacks the oxo ligand. Loss of chloride to give $\text{Et}_3\text{P=O}$ in combination with deprotonation of a neopentylidene ligand by triethylphosphine, probably in a cationic species, then leads to the observed products. In chlorobenzene a minor product of the reaction was found to be the blue salt $[\text{Et}_3\text{PH}][\text{W}(\text{C-t-Bu})\text{Cl}_4]$. It was found that the analogous tetraethylammonium salt could be prepared from $\text{W}(\text{C-t-Bu})(\text{CH}_2\text{-t-Bu})_3$ by treating it with ethereal HCl in the presence of tetraethylammonium chloride in ether. An important observation was that the reaction between $[\text{Et}_4\text{N}][\text{W}(\text{C-t-Bu})\text{Cl}_4]$ and 3 equivalents of lithium t-butoxide gave $\text{W}(\text{C-t-Bu})(\text{O-t-Bu})_3$, a pale yellow, pentane-soluble, thermally stable, and sublimable species. Most importantly, in terms of alkyne metathesis, this tri-t-butoxide complex would react rapidly with alkynes to give new analogous alkylidyne species. In fact, $\text{W}(\text{C-t-Bu})(\text{O-t-Bu})_3$ would metathesize unsymmetrical internal alkynes such as 3-

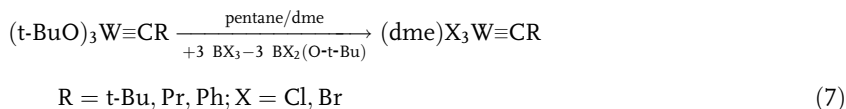
heptyne with remarkable facility at room temperature. This was the first time that a highly active and identifiable alkyne metathesis catalyst had been prepared.

When $(\text{Me}_3\text{CCH}_2)_3\text{W}\equiv\text{CCMe}_3$ is treated with 3 equivalents of HCl in ether in the presence of several equivalents of dimethoxyethane, the blue dimethoxyethane adduct shown in Eq. (6) is formed [23]. It was proposed that the neopentylidyne ligand is actually protonated



to give a neopentylidene ligand, which is subsequently turned into a neopentylidyne ligand by α hydrogen abstraction. Two more steps of this type would lead to removal of three neopentyl groups and to the observed product. $\text{W}(\text{C-t-Bu})\text{Cl}_3(\text{dme})$ was shown to react readily with LiX ($\text{X} = \text{O-t-Bu}$, NMe_2) or S-t-Bu to yield $\text{W}(\text{C-t-Bu})\text{X}_3$ complexes. These species were proposed to be monomers on the basis of their volatility and on the fact that $\text{W}(\text{C-t-Bu})(\text{NMe}_2)_3$ reacts with methanol to give dimeric species that contain bridging methoxides. It became clear that bulky groups were required in order to maintain the monomeric nature of these electron-deficient species (12 electrons, not including π donation).

It should be noted that a method of synthesizing compounds of the type $\text{W}(\text{CR})\text{X}_3(\text{dme})$ in good to excellent yields as shown in Eq. (7) has been reported [24]. This method is appealing in view of the fact that the starting $(\text{t-BuO})_3\text{W}\equiv\text{CR}$ complexes are readily available from the reaction between $(\text{t-BuO})_3\text{W}\equiv\text{W}(\text{O-t-Bu})_3$ and $\text{RC}\equiv\text{N}$ (to give $(\text{t-BuO})_3\text{W}\equiv\text{CR}$ plus insoluble $(\text{t-BuO})_3\text{W}\equiv\text{N}$) or excess $\text{RC}\equiv\text{CMe}$ (to give $(\text{t-BuO})_3\text{W}\equiv\text{CR}$ and $\text{MeC}\equiv\text{CMe}$), as described later. The synthesis of $\text{W}(\text{C-t-Bu})\text{Cl}_3(\text{dme})$ via $(\text{Me}_3\text{CCH}_2)_3\text{W}\equiv\text{CCMe}_3$ is still the shortest [25] (three steps from tungsten hexachloride), although $(\text{Me}_3\text{CCH}_2)_3\text{W}\equiv\text{CCMe}_3$ must be isolated by distillation and the method is relatively costly in terms of neopentyl groups.



The trichloride complex $\text{W}(\text{C-t-Bu})\text{Cl}_3(\text{dme})$ served as a starting point for synthesizing a wide variety of $\text{W}(\text{C-t-Bu})\text{X}_3$ species, especially those where X is a bulky alkoxide such as OCMe_3 , $\text{OCMe}(\text{CF}_3)_2$, $\text{OCMe}_2(\text{CF}_3)$, $\text{O-2,6-i-Pr}_2\text{C}_6\text{H}_3$, or $\text{O-2,6-Me}_2\text{C}_6\text{H}_3$ [14]. Complexes that contain smaller alkoxides can be prepared if 1 or 2 equivalents of a donor ligand are also bound to the metal. As an example, $\text{W}(\text{C-t-Bu})(\text{O-2,6-i-Pr}_2\text{C}_6\text{H}_3)_3$ is obtained free of THF, but the attempted synthesis of $\text{W}(\text{C-t-Bu})(\text{O-2,6-Me}_2\text{C}_6\text{H}_3)_3$ yielded $\text{W}(\text{C-t-Bu})(\text{O-2,6-Me}_2\text{C}_6\text{H}_3)_3(\text{THF})$ in-

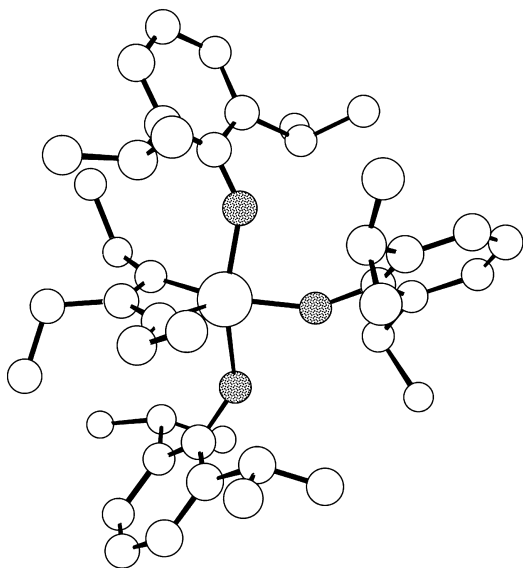


Fig. 1.11-1. Drawing of the structure of $W(C_3Et_3)(O-2,6-i-Pr_2C_6H_3)_3$.

stead [26]. Similarly, attempts to prepare $\text{W}(\text{C}-t\text{-Bu})[\text{OCH}(\text{CF}_3)_2]_3$ yielded $\text{W}(\text{C}-t\text{-Bu})[\text{OCH}(\text{CF}_3)_2]_3(\text{dme})$ instead [27]. Four-coordinate compounds that contain bulky alkoxides are often soluble in pentane. *t*-Butoxide complexes have been shown to be monomers (e.g., $\text{W}(\text{CPh})(\text{O}-t\text{-Bu})_3$ [28]) or weakly associated dimers (via a bridging *t*-butoxide ligand, as in $\text{W}(\text{CMe})(\text{O}-t\text{-Bu})_3$ [29]).

Tungsten alkylidyne tri-*t*-butoxide complexes react rapidly with many ordinary internal alkynes to give new alkylidyne complexes. Employing an excess of alkyne can drive the reaction to completion [30, 31]. However, no metallacyclobutadiene intermediates are observed, presumably because the *t*-butoxide ligand is relatively electron donating (and the metal therefore not sufficiently electrophilic) and sterically bulky.

In contrast, metallacyclobutadiene complexes are often observed when the alkoxide is more electron withdrawing, and especially when it is also relatively small. For example, excess 3-hexyne reacts with $W(C-t-Bu)(O-2,6-i-Pr_2C_6H_3)_3$ to yield $t-BuC\equiv CEt$ and the tungstacyclobutadiene complex $W(C_3Et_3)(O-2,6-i-Pr_2C_6H_3)_3$ [26]. As shown in Figure 1.11-1, this sterically crowded molecule is approximately a trigonal bipyramid with a planar tungstacyclobutadiene ring located in the equatorial position; the two $W-C_\alpha$ bond lengths are 1.883(10) Å and 1.949(9) Å. Interestingly, the $W-C_\beta$ bond distance is only 2.159(10) Å, which is actually of the order or even shorter than a typical $W-C$ single bond. $W(C_3Et_3)(O-2,6-i-Pr_2C_6H_3)_3$ will catalyze the metathesis of 3-heptyne, and it reacts with 3-hexyne- d_{10} at a rate that is independent of the concentration of 3-hexyne- d_{10} , characteristic of rate-limiting loss of 3-hexyne from the tungstacyclobutadiene ring. Tungstacyclobutadiene complexes are also obtained when the alkoxide is $OCH(CF_3)_2$ or $OCMe(CF_3)_2$ [27].

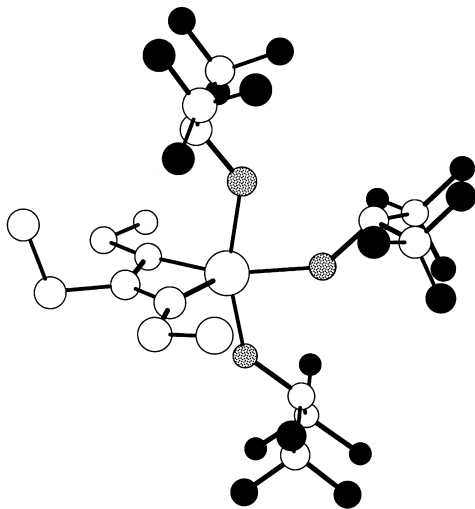
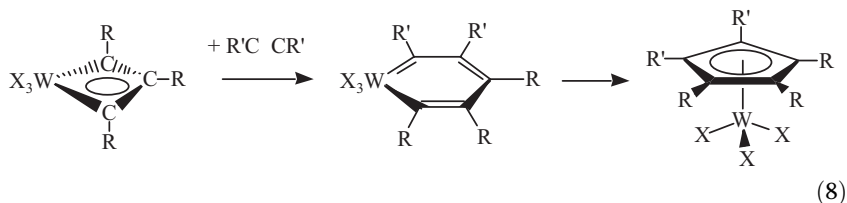


Fig. 1.11-2. Drawing of the structure of $W(C_3Et_3)[OCH(CF_3)_2]_3$.

An X-ray structure of one example ($OR = OCH(CF_3)_2$, Figure 1.11-2) showed it to be virtually indistinguishable from the structure of $W(C_3Et_3)(O-2,6-i-Pr_2C_6H_3)_3$. Interestingly, $W(C_3R_3)(OR')_3$ species will metathesize alkynes when $OR' = OCH(CF_3)_2$ or $OCMe(CF_3)_2$, but by different mechanisms. $W(C_3Et_3)[OCMe(CF_3)_2]_3$ catalyzes the metathesis of alkynes rapidly by a dissociative mechanism, while $W(C_3Et_3)[OCH(CF_3)_2]_3$ catalyzes the metathesis of alkynes relatively slowly in non-coordinating solvents by an associative mechanism, one that was proposed to proceed via intermediate metallacyclohexatriene complexes (Eq. (8)). In this alternative mechanism, there is a risk of forming a cyclopentadienyl complex irreversibly, a reaction that has been documented for trichloride complexes (see later). Interestingly, in diethyl ether $W(C_3Et_3)[OCH(CF_3)_2]_3$ will catalyze the metathesis of alkynes relatively rapidly, possibly because ether assists in breaking up the metal-lacetyne to yield $W(CR)[OCH(CF_3)_2]_3(ether)_x$ species ($x = 1$ or 2).

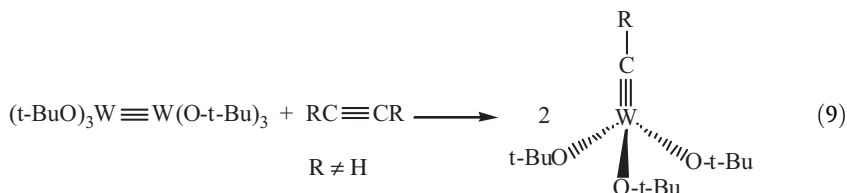


1.11.4

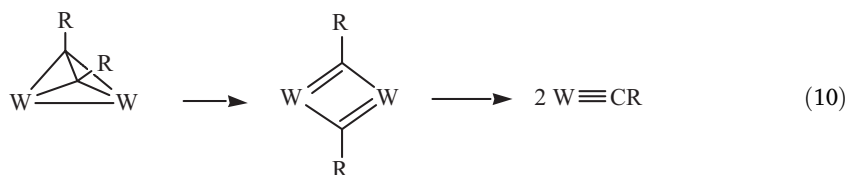
Formation of Trialkoxy Alkylidyne Complexes from $W_2(OR)_6$ Species

An efficient method of preparing a wide variety of $(t-BuO)_3W\equiv CR$ complexes is the reaction between $W_2(O-t-Bu)_6$ and $RC\equiv CR$, as shown in Eq. (9) [32, 33]. This

remarkable reaction is believed to proceed via a species having a W_2C_2 “dimetalla-tetrahedrane” core in which



there are only single bonds between any pair of atoms. (DFT calculations [34] suggest that the lowest energy pathway involves a “flattening” of the ditungstatetrahedrane to give a 1,3-ditungstacyclobutadiene complex, which dissociates into 2 equivalents of the trialkoxytungsten alkylidyne complex [Eq. (10)].) For example, addition of slightly more than 1 equivalent of 2-butyne, 3-hexyne, or 4-octyne to $W_2(O\text{-}t\text{-Bu})_6$ gives $(t\text{-BuO})_3W \equiv CR$ ($R = \text{Me}$, Et , or Pr) in high yield. $W_2(O\text{-}t\text{-Bu})_6$ does not react readily with $RC \equiv CR$ when $R = t\text{-Bu}$, SiMe_3 , SnMe_3 , or Ph [33], probably for largely steric reasons. Addition of excess $\text{MeC} \equiv \text{C}\text{-}t\text{-Bu}$ to



$W_2(O\text{-}t\text{-Bu})_6$ produces $(t\text{-BuO})_3W \equiv \text{C}\text{-}t\text{-Bu}$ cleanly if the 2-butyne that is formed is removed under a slight vacuum [33]. Attempted reactions that involve terminal alkynes and acetylene itself usually produce bimetallic species having a metal-metal bond instead of monomeric alkylidyne complexes [35–37].

The reaction between an alkyne and $W_2(O\text{-}t\text{-Bu})_6$ presented the opportunity of preparing and studying functionalized alkylidyne complexes, some of which are inaccessible using other approaches. For example, the reaction between $W_2(O\text{-}t\text{-Bu})_6$ and $RC \equiv CR$ yields $(t\text{-BuO})_3W \equiv CR$ when $R = \text{CH}_2\text{NR}'_2$ or $\text{CH}_2\text{OR}'$, while the reaction between $W_2(O\text{-}t\text{-Bu})_6$ and 2 equivalents of $\text{MeC} \equiv \text{CR}$ yields $(t\text{-BuO})_3W \equiv CR$ when $R = \text{CH}_2\text{CO}_2\text{Me}$ or $\text{S}\text{-}t\text{-Bu}$ [33]. Directly functionalized alkynes such as $\text{Et}_2\text{NC} \equiv \text{CNEt}_2$ generally do not react cleanly with $W_2(O\text{-}t\text{-Bu})_6$ to give alkylidyne complexes. No effort was made to determine the extent to which tungsten tri-*t*-butoxide complexes would metathesize various functionalized alkynes.

Although many other $W_2(OR)_6$ compounds can be prepared, few react with internal alkynes to yield alkylidyne complexes. $W_2[\text{OCMe}_2(\text{CF}_3)]_6$ reacts with 2-butyne or 3-hexyne to yield alkylidyne complexes [38], but the reaction between $W_2(O\text{-}2,6\text{-Me}_2\text{C}_6\text{H}_3)_6$ and internal alkynes produces tungstacyclobutadiene complexes [39]. These particular metallacycles do not appear to serve as long-lived catalysts for the metathesis of alkynes.

Nitriles also react cleanly with $W_2(O-t-Bu)_6$ to produce $(t-BuO)_3W\equiv CR$ and the polymeric nitride $[(t-BuO)_3W\equiv N]_x$, which is easily removed by filtration [33]. The disadvantage of this method is that the yield of alkylidyne is limited to 50%. Other $W_2(OR)_6$ species generally do not react smoothly with nitriles to give $(RO)_3W\equiv CR'$ complexes. A potential limitation of this type is the (usually relatively slow) Wittig-like reaction between $(RO)_3W\equiv CR'$ and $R'C\equiv N$ to give $[(t-BuO)_3W\equiv N]_x$ and $R'C\equiv CR'$.

1.11.5

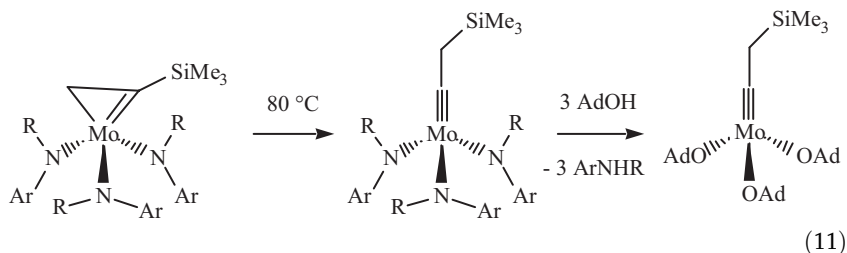
Alkylidyne Complexes of Molybdenum

The chemistry of high oxidation state molybdenum alkylidyne complexes has closely paralleled the chemistry of tungsten alkylidyne complexes. However, molybdenum chemistry has been limited by the poor yield of $(Me_3CCH_2)_3Mo\equiv CCMe_3$ (<35%) that is obtained upon adding MoO_2Cl_2 to $t-BuCH_2MgCl$ in THF [40, 41] and by the fact that the yield appears to decrease upon scaling up the reaction. Nevertheless, once $(Me_3CCH_2)_3Mo\equiv CCMe_3$ has been prepared, it is a well-behaved species that reacts with HCl in ether in the presence of dimethoxyethane to give $Mo(C-t-Bu)Cl_3(dme)$ quantitatively. From this species a wide variety of molybdenum neopentylidyne complexes of the type $Mo(C-t-Bu)(OR)_3$ ($OR = O-t-Bu$, $OCMe(CF_3)_2$, $OCH(CF_3)_2$, $OCMe_2(CF_3)$, or $O-2,6-i-Pr_2C_6H = DIPP$) were prepared [41], as well as carboxylates [42] and thiolates [43]. Interestingly, molybdenum t-butoxide complexes are relatively poor catalysts for alkyne metathesis (at room temperature), while carboxylates and thiolates are inactive. $Mo(CR)(DIPP)_3$ complexes are good catalysts for the metathesis of alkynes, and one molybdacyclobutadiene complex, $Mo(C_3Et_3)(DIPP)_3$, has been observed in NMR spectra at low temperatures, although it is not stable enough with respect to loss of alkyne from the ring to be isolated. Molybdenum complexes that contain fluoroalkoxides will metathesize internal alkynes at a rate that correlates with the size and electron-withdrawing properties of the alkoxide ligands [41]. For example, $Mo(C-t-Bu)[OCH(CF_3)_2]_3(dme)$ will metathesize 3-heptyne at room temperature, although alkynes, especially 2-butyne, are also polymerized. The alkoxide ligands in $Mo(C-t-Bu)[OCMe_2(CF_3)]_3$ are bulky enough to prevent polymerization, but the metal is not electrophilic enough to metathesize 3-heptyne efficiently. On the other hand, Mo catalysts that contain hexafluoro-t-butoxide ligands will metathesize 3-heptyne rapidly.

Dimolybdenum hexa-t-butoxide does not react with internal alkynes to form alkylidyne complexes. It does react with terminal alkynes to form $Mo(CR)(O-t-Bu)_3$ complexes, although only in poor yield. $Mo(CPr)(O-t-Bu)_3$ and $Mo(CPh)(O-t-Bu)_3$ have been prepared in this manner from 1-pentyne and phenylacetylene, respectively [44]. These reactions are not as clean as the analogous reactions for tungsten species because oligomerization and polymerization of the terminal acetylenes compete with the formation of alkylidyne complexes.

A potentially general route to molybdenum trialkoxide alkylidyne complexes in-

volves the rearrangement of η^2 -vinyl species. The η^2 -vinyl species shown in Eq. (11) was found to rearrange to the alkylidyne complex via a 1,2 migration of the trimethylsilyl group (Ar = 3,5-dimethylphenyl, R = isopropyl) [45]. Upon addition of 3 equivalents of 1-adamantanol, the triadamantoxo (AdO) alkylidyne complex could be isolated as a crystalline solid. An X-ray



structural study showed the Mo=C bond length to be 1.754(6) Å. The (AdO)₃Mo(CCH₂SiMe₃) complex reacts readily with 3-hexyne or 2-butyne to yield (AdO)₃Mo(CR) (R = Et or Me) and was shown to metathesize MeC≡CCH₂CH₂OTs to yield TsOCH₂CH₂C≡CCH₂CH₂OTs and 2-butyne. This route to adamantoxo molybdenum alkylidyne complexes is longer than that based upon (Me₃CCH₂)₃Mo≡CCMe₃, but it is potentially more reliable and can be scaled up. Although only adamantoxo derivatives have been insoluble enough to isolate in pure form, it might be possible to replace the adamantoxo ligands with halides (Eq. (7)) and thereby gain access to a variety of trialkoxide species.

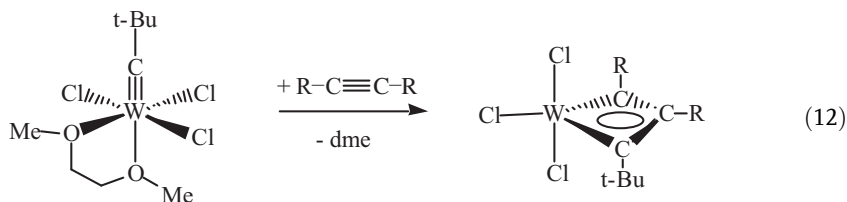
1.11.6

Reactions that Limit Metathesis Activity

Like most homogeneous catalytic reactions, the alkyne metathesis reaction is finely balanced and may fail for a variety of reasons, as outlined in this section.

Sterically bulky alkoxides appear to be crucial for long-lived metathesis reactions. They prevent bimolecular reactions in general, e.g., formation of dimetallatetrahedrane species or decomposition products that result from bimolecular ligand redistributions. Relatively more electron-donating bulky ligands (C-, N-, or S-based) do not support metathesis. For example, W(C-*t*-Bu)(CH₂-*t*-Bu)₃, W(C-*t*-Bu)(NMe₂)₃ [23], and W(C-*t*-Bu)(SR)₃ [23, 43] do not react readily with terminal or internal alkynes. However, W(C-*t*-Bu)(N-*i*-Pr)₃ has been claimed to metathesize phenyltolylacetylene [5]. An impurity such as W(C-*t*-Bu)(N-*i*-Pr)₂Cl or W(C-*t*-Bu)(N-*i*-Pr)₂Cl₂ therefore actually may be responsible for the observed activity.

Reactions between W(C-*t*-Bu)Cl₃(dme) and internal alkynes (Eq. (12)) illustrate that although tungstenacyclobutadiene complexes [46], W[C(*t*-Bu)C(R)C(R)]Cl₃, can be isolated (and shown to be trigonal bipyramidal species analogous to the structures shown in Figures 1.11-1 and 1.11-2) [47], these species react with an additional equivalent of alkyne to yield what is presumed to be an intermediate cyclopentadienyl complex, W[η^5 -C₅(*t*-Bu)R₄]Cl₃ (Eq. (8)), which



disproportionates to yield 0.5 equivalents of $W[\eta^5-C_5(t-Bu)R_4]Cl_4$ and (with another 0.5 equivalents of $RC\equiv CR$) 0.5 equivalents of $W[\eta^5-C_5(t-Bu)R_4](RC\equiv CR)Cl_2$ [48]. Therefore, formation of metallacyclobutadiene complexes is not sufficient for catalytic alkyne metathesis. In the case of $W[C(t-Bu)C(R)C(R)]Cl_3$, there is no steric impetus to lose alkyne, and the metal is still sterically accessible for more alkyne to coordinate. Formation of the cyclopentadienyl ring amounts to a “reduction” of the metal by two electrons if the alkylidyne ligand is counted as a trianionic ligand.

η^3 -Cyclopropenyl complexes are viable alternatives to planar metallacyclobutadiene complexes. For example, addition of tetramethylethylenediamine to $W[C(t-Bu)C(Me)C(Me)]Cl_3$ leads to the η^3 -cyclopropenyl complex shown in Figure 1.11-3 [48–50]. Triscarboxylate species also react with alkynes to yield η^3 -cyclopropenyl complexes [42]. An η^3 -cyclopropenyl complex can be induced to lose an alkyne upon replacing the carboxylate ligands with alkoxides. Since a compound that contains a localized, non-planar metallacyclobutadiene ring also has been isolated (Figure 1.11-4), all variations of $M(C_3R_3)$ species must be considered as viable structures in an alkyne metathesis system, although planar metallacyclo-

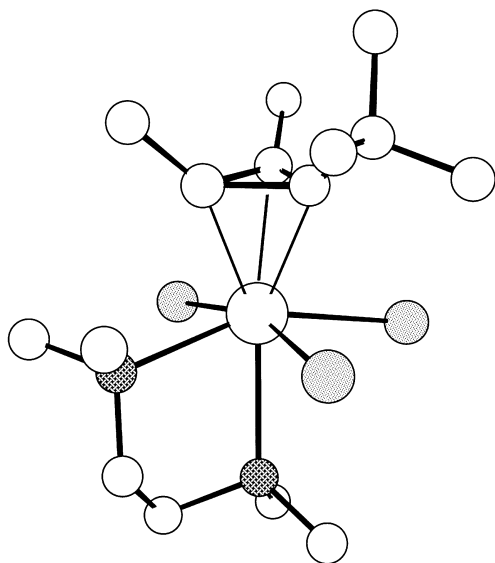


Fig. 1.11-3. Drawing of the structure of $W[\eta^3-C(t-Bu)C(Me)C(Me)](Me_2NCH_2CH_2NMe_2)Cl_3$.

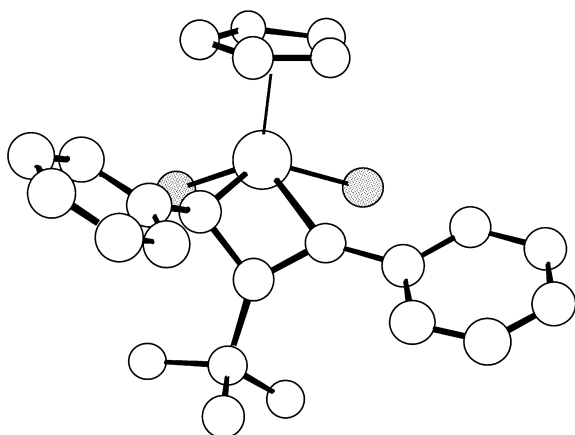
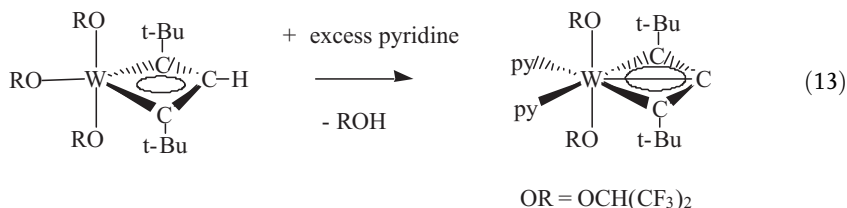


Fig. 1.11-4. Drawing of the structure of $\text{W}(\eta^5\text{-C}_5\text{H}_5)[\text{C}(\text{Ph})\text{C}(\text{t-Bu})\text{C}(\text{Ph})]\text{Cl}_2$.

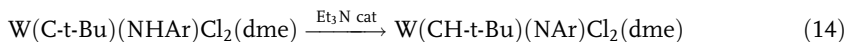
butadiene complexes so far have been the lowest energy species in a functioning metathesis system.

Metathesis activity of terminal alkynes is limited [51] for several reasons. One is that only α,α' -disubstituted metallacyclobutadiene complexes may form, intermediates that would lead to only degenerate metathesis. Second, although α,α' -disubstituted metallacycles can be isolated ($\text{W}[\text{C}(\text{t-Bu})\text{CHC}(\text{t-Bu})][\text{OCH}(\text{CF}_3)_2]_3$ [52] has been structurally characterized [47]), they tend to lose the β proton to yield “ β -deprotiometallacyclobutadiene” complexes, especially in the presence of donor ligands (e.g., Eq. (13)). Third, methylidyne complexes are relatively unstable with respect to bimolecular formation of dimetallatetrahedrane species [33, 35]. A fourth reason is that acetylene that is generated as a metathesis product is likely to be much more reactive (and in unique ways) than a disubstituted alkyne. Finally, polymerization of terminal alkynes is a significant side reaction [51, 53].



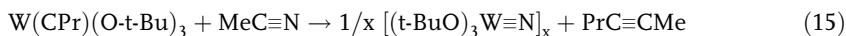
Alkylidyne complexes can be protonated to give stable alkylidene complexes if the conjugate base that is produced in the process is a good σ and π electron donor. For example, $\text{W}(\text{C-t-Bu})\text{Cl}_3(\text{dme})$ reacts with Me_3SiNHAr (e.g., $\text{Ar} = 2,6\text{-i-Pr}_2\text{C}_6\text{H}_3$) to yield amido neopentylidyne complexes that can be transformed into imido neopentylidene complexes by catalytic amounts of triethylamine (Eq. (14)). Imido alkylidene species are valuable intermediates in the synthesis of a wide variety of

olefin metathesis catalysts. (See another chapter in this volume.) A proton can be transferred from the amido nitrogen to the alkylidyne carbon atom in the presence of highly electron-withdrawing (e.g., halide) ligands but not alkoxide ligands. For example, $M(C\text{-}t\text{-Bu})(NHAr)(OR)_2$ complexes have been prepared [54], but

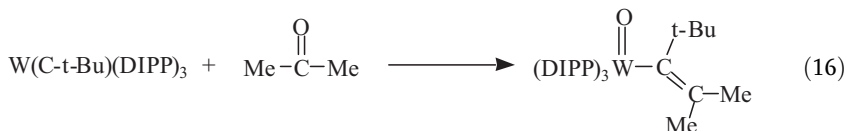


they cannot be transformed into their imido neopentylidene analogues with triethylamine. Amido alkylidyne bisalkoxide complexes also do not react readily with internal alkynes, perhaps as a consequence of the amido group donating too much electron density to the metal.

Some tungsten alkylidyne complexes are known to react with nitriles slowly to give nitrides (e.g., Eq. (15)). However, complexes that contain a nitrile functionality, e.g.,



$W(CCH_2CN)(O\text{-}t\text{-Bu})_3(py)$ [33] and $W(C\text{-}t\text{-Bu})(O\text{-}2,6\text{-}i\text{-}Pr_2C_6H_3)_3(t\text{-BuCN})$ [55], are also known. Yet $W_2(O\text{-}t\text{-Bu})_6$ reacts with $EtC\equiv CCN$ in the presence of quinclidine to form $W(CC\equiv CEt)(O\text{-}t\text{-Bu})_3(quin)$ and the nitride instead of $W(CCN)(O\text{-}t\text{-Bu})_3(quin)$ and $W(CEt)(O\text{-}t\text{-Bu})_3(quin)$. Other “Wittig-like” reactions include the reaction shown in Eq. (16) [56].



Analogous reactions are observed for benzaldehyde, formaldehyde, N,N' -dimethylformamide, and ethyl formate. $W(C\text{-}t\text{-Bu})Cl_3(dme)$ also has been shown to react with 2 equivalents of cyclohexylisocyanate to form an oxazetin tungstacycle, $W[N(Cy)C(C(t\text{-Bu})=C=O)O]Cl_3(NCy)$ [57].

Other protonations of alkylidyne complexes have been documented. For example, $W(C\text{-}t\text{-Bu})(O\text{-}t\text{-Bu})_3$ reacts with 2 equivalents of an HX acid ($HX = HCl, HBr$, a phenol, or RCO_2H) to give complexes of the type $W(CH\text{-}t\text{-Bu})(O\text{-}t\text{-Bu})_2X_2$ [58], species that are analogous to the alkylidene complexes prepared and studied by Osborn [59–61]. Several brief studies have shown that some neopentylidyne complexes react with water to form oxo alkyl complexes [62–64]. Such reactions are likely to be irreversible and any alkyne metathesis activity therefore halted.

It is interesting to note that no reactions between alkyne metathesis catalysts and ordinary olefins have been reported and that $W_2(O\text{-}t\text{-Bu})_6$ is known to react with excess $EtC\equiv CCH=CH_2$ to give $W(CCH=CH_2)(O\text{-}t\text{-Bu})_3$ [33]. Recently it has been reported that alkynes can be metathesized in the presence of olefins by $Mo(CO)_6$ /phenol systems [65].

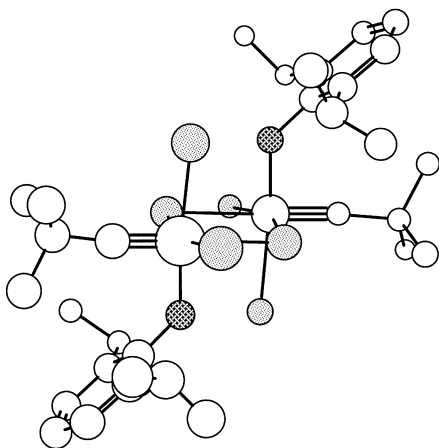
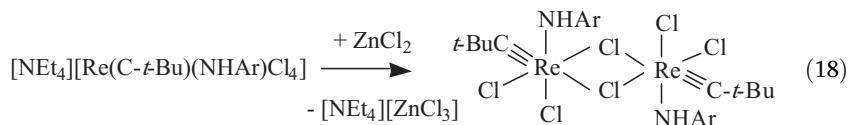
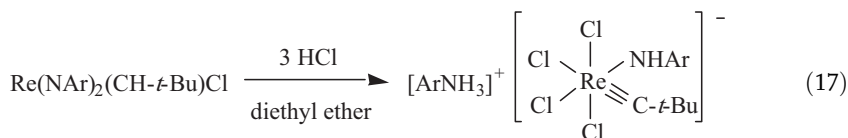


Fig. 1.11-5. Drawing of the structure of $[\text{Re}(\text{C-}t\text{-Bu})(\text{NHAr})\text{Cl}_3]_2$.

1.11.7

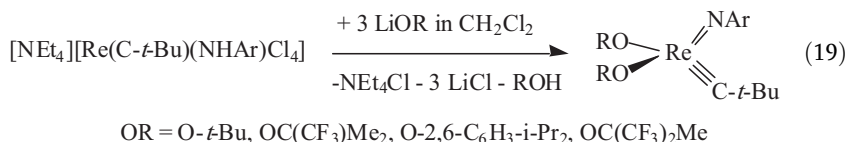
Alkylidyne Complexes of Rhenium

Rhenium imido alkylidyne complexes have been prepared and shown to behave as alkyne metathesis catalysts, but not without significant limitations [66, 67]. $\text{Re}(\text{NAr})_2(\text{CH-}t\text{-Bu})\text{Cl}$ ($\text{Ar} = 2,6\text{-}i\text{-Pr}_2\text{C}_6\text{H}_3$) reacts with 3 equivalents of HCl in diethyl ether to give $[\text{ArNH}_3][\text{Re}(\text{C-}t\text{-Bu})(\text{NHAr})\text{Cl}_4]$ as an insoluble orange powder (Eq. (17)), from which $[\text{NEt}_4][\text{Re}(\text{C-}t\text{-Bu})(\text{NHAr})\text{Cl}_4]$ could be prepared by cation exchange. Addition of ZnCl_2 to $[\text{NEt}_4][\text{Re}(\text{C-}t\text{-Bu})(\text{NHAr})\text{Cl}_4]$ gave $[\text{Re}(\text{C-}t\text{-Bu})(\text{NHAr})\text{Cl}_3]_2$ (Eq. (18)), an X-ray study of which (Figure 1.11-5) showed it to be a dimer in which each Re is a square pyramid with the neopentylidyne α



carbon atom in the apical position and a weakly bound bridging chloride ligand *trans* to the alkylidyne completes a six-coordinate geometry ($\text{Re}=\text{C} = 1.75(1) \text{ \AA}$, $\text{Re}=\text{C}-\text{C} = 165(1)^\circ$). Complexes of the type $\text{Re}(\text{C-}t\text{-Bu})(\text{NAr})(\text{OR})_2$ can be prepared from $[\text{NEt}_4][\text{Re}(\text{C-}t\text{-Bu})(\text{NHAr})\text{Cl}_4]$, as shown in Eq. (19). The $\text{Re}(\text{C-}t\text{-Bu})(\text{NAr})(\text{OR})_2$ species react with alkynes to yield two types of rhenacyclobutadiene

complexes, one of which readily loses alkyne and is active for the metathesis of alkynes. The labile rhenacyclobutadiene complex is formed



when an acetylene attacks a C/O/O face in Re(CR')(NAr)(OR)₂. Non-labile, metathesis inactive rhenacycles are formed when an acetylene attacks a C/N/O face. Only acetylenes containing bulky groups are metathesized for some period of time, and only complexes that contain OCMe(CF₃)₂ ligands are active at room temperature. The steric bulk of the acetylene groups and the alkoxides is believed to direct formation of the labile rhenacyclobutadiene intermediates and allow alkyne metathesis to proceed, until stable rhenacycles or Re(V) decomposition products are formed. These studies suggest that rhenium alkylidyne complexes of this type will not be viable as long-lived alkyne metathesis catalysts.

1.11.8

Conclusions and Comments

I believe it is clear from what has been presented here that certain complexes of the type M(CR)(OR')₃ (M = Mo, W; OR' = bulky and electron withdrawing) are viable and, in some cases, excellent catalysts for the metathesis of internal alkynes. Reactions in which alkylidyne species are highly reactive, but present in low concentration, and/or reactions in which alkylidyne complexes are formed at a steady rate from catalyst precursors also can be successful, even though the actual alkylidyne species cannot be observed. No alkyne metathesis by a well-defined "low oxidation state" species has been documented. Rapid alkyne metathesis therefore so far appears to be limited to high oxidation state Mo and W alkylidyne complexes.

The mechanism that involves metallacyclobutadiene intermediates (or variations such as distorted metallacycles or even η^3 -cyclopropenyl species) seems by far to be the most common, with a mechanism that involves a "metallacyclohexatriene" intermediate being the only viable alternative at this stage. The disadvantage of a metallacyclohexatriene intermediate is that it is susceptible to irreversible formation of a cyclopentadienyl ring. There is currently no evidence for viable mechanisms that involve two or more metals behaving in a cooperative manner, except to generate an initial monomeric alkylidyne complex.

Although it is impossible to say with any degree of certainty, it seems likely that the original heterogeneous catalysts (WO₃ on silica) contain an alkylidyne "tri-alkoxo" species (in which the "alkoxides" are surface oxides), the alkylidyne ligand being formed via some rearrangement or scission of the alkyne. The systems reported by Mortreux [3, 4] (and extended by Bunz; see the chapter in this volume)

employ $\text{Mo}(\text{CO})_6$ in a phenol. One can imagine that a $\text{Mo}(\text{CR})(\text{phenoxide})_3$ complex might be formed under these conditions with the initial alkylidyne coming from either CO or the alkyne itself.

In the past several years, Fürstner has explored some organic applications that involve alkyne metathesis (see Chapter 2.12). Although he employed $\text{WC-t-Bu}(\text{O-t-Bu})_3$ as an initiator initially, he has developed processes based upon Mo triamido complexes in dichloromethane. Again, it seems most likely that a high oxidation state species is responsible for the metathesis activity. A reaction that involves dichloromethane, either as the source of the initial alkylidyne or possibly also as an oxidizing agent, is not unreasonable. A plausible formulation is $\text{Mo}(\text{CR}')(\text{amido})\text{Cl}_2$. Possibly only a small fraction of the initial Mo(III) species is converted into the active species. In spite of the uncertainty concerning the nature of the catalyst, this system is attractive for organic applications as a consequence of its simplicity.

To date, applications of alkyne metathesis have not been nearly as numerous as applications of alkene metathesis. Although that situation seems unlikely to change dramatically, alkyne metathesis nevertheless could continue to be useful for certain transformations, especially those in which the new triple bond is employed in subsequent more traditional organic transformations or is selectively hydrogenated to a *cis* olefin.

Acknowledgments

I thank the National Science Foundation, for supporting research on multiple metal-carbon bonds for many years, and the many coworkers who have been involved in this research, for their hard work and enthusiasm.

References

- 1 PANNELLA, F.; BANKS, R. L.; BAILEY, G. C. *J. Chem. Soc., Chem. Commun.* **1968**, 1548.
- 2 MOULIJN, J. A.; REITSMA, H. J.; BOELHOUWER, C. *J. Catal.* **1972**, *25*, 434.
- 3 MORTREUX, A.; BLANCHARD, M. J. *Chem. Soc. Chem. Commun.* **1974**, 786.
- 4 MORTREUX, A.; DELGRANGE, J. C.; BLANCHARD, M.; LABOCHINSKY, B. J. *Molec. Catal.* **1977**, *2*, 73.
- 5 DEVARAJAN, S.; WALTON, O. R. M.; LEIGH, G. J. *J. Organometal. Chem.* **1979**, *181*, 99.
- 6 KATZ, T. J.; MCGINNIS, J. J. *Am. Chem. Soc.* **1975**, *97*, 1592.
- 7 HÉRISON, J. L.; CHAUVIN, Y. *Makromol. Chem.* **1971**, *141*, 161.
- 8 FISCHER, E. O.; KREIS, G.; KREITER, C. G.; MÜLLER, J.; HUTTNER, G.; LORENZ, H. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 564.
- 9 FISCHER, H.; HOFMANN, P.; KREISL, F. R.; SCHROCK, R. R.; SCHUBERT, U.; WEISS, K. *Carbyne Complexes*; VCH: Weinheim; New York, 1988.
- 10 KREISL, F. R., Ed. *Transition Metal Carbyne Complexes*; Kluwer Academic Publishers: Dordrecht/Boston/London, 1992.
- 11 SCHROCK, R. R. *J. Organometal. Chem.* **1986**, *300*, 249.
- 12 SCHROCK, R. R. *Acc. Chem. Res.* **1986**, *19*, 342.
- 13 SCHROCK, R. R. *Chem. Rev.* **2002**, *102*, 145.

- 14 MURDZEK, J. S.; SCHROCK, R. R. In *Carbyne Complexes*; VCH: New York, 1988.
- 15 GUGGENBERGER, L. J.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1975**, *97*, 2935.
- 16 McLAIN, S. J.; WOOD, C. D.; MESSERLE, L. W.; SCHROCK, R. R.; HOLLANDER, F. J.; YOUNGS, W. J.; CHURCHILL, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 5962.
- 17 CHURCHILL, M. R.; YOUNGS, W. J. *Inorg. Chem.* **1979**, *18*, 171.
- 18 FELLMANN, J. D.; TURNER, H. W.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1980**, *102*, 6608.
- 19 SCHROCK, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796.
- 20 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, 1997.
- 21 CLARK, D. N.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1978**, *100*, 6774.
- 22 SCHROCK, R. R.; SEIDEL, S. W.; MÖSCH-ZANETTI, N. C.; DOBBS, D. A.; SHIH, K.-Y.; DAVIS, W. M. *Organometallics* **1997**, *16*, 5195.
- 23 SCHROCK, R. R.; CLARK, D. N.; SANCHO, J.; WENGROVIUS, J. H.; ROCKLAGE, S. M.; PEDERSEN, S. F. *Organometallics* **1982**, *1*, 1645.
- 24 STEVENSON, M. A.; HOPKINS, M. D. *Organometallics* **1997**, *16*, 3572.
- 25 SCHROCK, R. R.; SANCHO, J.; PEDERSEN, S. F. *Inorg. Syn.* **1989**, *26*, 44.
- 26 CHURCHILL, M. R.; ZILLER, J. W.; FREUDENBERGER, J. H.; SCHROCK, R. R. *Organometallics* **1984**, *3*, 1554.
- 27 FREUDENBERGER, J. H.; SCHROCK, R. R.; CHURCHILL, M. R.; RHEINGOLD, A. L.; ZILLER, J. W. *Organometallics* **1984**, *3*, 1563.
- 28 COTTON, F. A.; SCHWOTZER, W.; SHAMSHOUM, E. S. *Organometallics* **1984**, *3*, 1770.
- 29 CHISHOLM, M. H.; HOFFMAN, D. M.; HUFFMAN, J. C. *Inorg. Chem.* **1983**, *22*, 2903.
- 30 WENGROVIUS, J. H.; SANCHO, J.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3932.
- 31 SANCHO, J.; SCHROCK, R. R. *J. Molec. Catal.* **1982**, *15*, 75.
- 32 SCHROCK, R. R.; LISTEMANN, M. L.; STURGEON, L. G. *J. Am. Chem. Soc.* **1982**, *104*, 4291.
- 33 LISTEMANN, M. L.; SCHROCK, R. R. *Organometallics* **1985**, *4*, 74.
- 34 FANTACCI, S.; RE, N.; ROSI, M.; SGAMELLOTTI, A.; GUEST, M. F.; SHERWOOD, P.; FLORIANI, C. *J. Chem. Soc., Dalton Trans.* **1997**, 3845.
- 35 CHISHOLM, M. H.; FOLTING, K.; HOFFMAN, D. M.; HUFFMAN, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6794.
- 36 CHISHOLM, M. H.; HUFFMAN, J. C.; HOFFMAN, D. M. *Chem. Soc. Rev.* **1985**, *14*, 69.
- 37 CHISHOLM, M. H. *Acc. Chem. Res.* **1990**, *23*, 419.
- 38 FREUDENBERGER, J. H.; PEDERSEN, S. F.; SCHROCK, R. R. *Bull. Soc. Chim. Fr.* **1985**, 349.
- 39 LATHAM, I. A.; SITA, L. R.; SCHROCK, R. R. *Organometallics* **1986**, *5*, 1508.
- 40 MCCULLOUGH, L. G.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 4067.
- 41 MCCULLOUGH, L. G.; SCHROCK, R. R.; DEWAN, J. C.; MURDZEK, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5987.
- 42 SCHROCK, R. R.; MURDZEK, J. S.; FREUDENBERGER, J. H.; CHURCHILL, M. R.; ZILLER, J. W. *Organometallics* **1986**, *5*, 25.
- 43 MURDZEK, J. S.; BLUM, L.; SCHROCK, R. R. *Organometallics* **1988**, *7*, 436.
- 44 STRUTZ, H.; SCHROCK, R. R. *Organometallics* **1984**, *3*, 1600.
- 45 TSAI, Y. C.; DIACONESCU, P. L.; CUMMINS, C. C. *Organometallics* **2000**, *19*, 5260.
- 46 PEDERSEN, S. F.; SCHROCK, R. R.; CHURCHILL, M. R.; WASSERMAN, H. J. *J. Am. Chem. Soc.* **1982**, *104*, 6808.
- 47 CHURCHILL, M. R.; WASSERMAN, H. J. *J. Organomet. Chem.* **1984**, *270*, 201.
- 48 SCHROCK, R. R.; PEDERSEN, S. F.; CHURCHILL, M. R.; ZILLER, J. W. *Organometallics* **1984**, *3*, 1574.
- 49 CHURCHILL, M. R.; FETTINGER, J. C.; MCCULLOUGH, L. G.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 3356.
- 50 CHURCHILL, M. R.; ZILLER, J. W.; PEDERSEN, S. F.; SCHROCK, R. R. *J. Chem. Soc., Chem. Commun.* **1984**, 485.
- 51 BRAY, A.; MORTREUX, A.; PETIT, F.;

- PETIT, M.; SZYMANSKA-BUZAR, T. J. *Chem. Soc., Chem. Commun.* **1993**, 197.
- 52 FREUDENBERGER, J. H.; SCHROCK, R. R. *Organometallics* **1986**, 5, 1411.
- 53 STRUTZ, H.; DEWAN, J. C.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1985**, 107, 5999.
- 54 SCHROCK, R. R.; DEPUE, R.; FELDMAN, J.; SCHAUVERIEN, C. J.; DEWAN, J. C.; LIU, A. H. *J. Am. Chem. Soc.* **1988**, 110, 1423.
- 55 FREUDENBERGER, J. H., Ph.D. Thesis, 1986, Massachusetts Institute of Technology.
- 56 FREUDENBERGER, J. H.; SCHROCK, R. R. *Organometallics* **1986**, 5, 398.
- 57 WEISS, K.; SCHUBERT, U.; SCHROCK, R. R. *Organometallics* **1986**, 5, 397.
- 58 FREUDENBERGER, J. H.; SCHROCK, R. R. *Organometallics* **1985**, 4, 1937.
- 59 KRESS, J.; WESOLEK, M.; OSBORN, J. A. *J. Chem. Soc. Chem. Commun.* **1982**, 514.
- 60 KRESS, J.; OSBORN, J. A. *J. Am. Chem. Soc.* **1983**, 105, 6346.
- 61 KRESS, J.; AGUERO, A.; OSBORN, J. A. *J. Mol. Catal.* **1986**, 36, 1.
- 62 FEINSTEIN-JAFFE, I.; PEDERSEN, S. F.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1983**, 105, 7176.
- 63 FEINSTEIN-JAFFE, I.; GIBSON, D.; LIPPARD, S. J.; SCHROCK, R. R.; SPOOL, A. J. *J. Am. Chem. Soc.* **1984**, 106, 6305.
- 64 FEINSTEIN-JAFFE, I.; DEWAN, J. C.; SCHROCK, R. R. *Organometallics* **1985**, 4, 1189.
- 65 BRIZIUS, G.; PSCHIRER, N. G.; STEFFEN, W.; STITZER, K.; LOYE, H.-C. Z.; BUNZ, U. H. F. *J. Am. Chem. Soc.* **2000**, 122, 12435.
- 66 SCHROCK, R. R.; WEINSTOCK, I. A.; HORTON, A. D.; LIU, A. H.; SCHOFIELD, M. H. *J. Am. Chem. Soc.* **1988**, 110, 2686.
- 67 WEINSTOCK, I. A.; SCHROCK, R. R.; DAVIS, W. M. *J. Am. Chem. Soc.* **1991**, 112, 135.

1.12

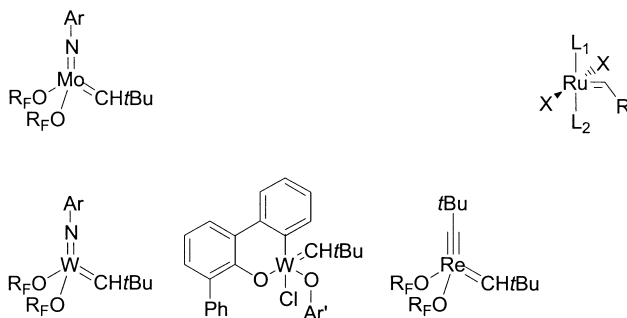
Well-Defined Metallocarbenes and Metallocarbynes Supported on Oxide Supports Prepared via Surface Organometallic Chemistry: A Source of Highly Active Alkane, Alkene, and Alkyne Metathesis Catalysts

Christophe Copéret, Frédéric Lefebvre, and Jean-Marie Basset

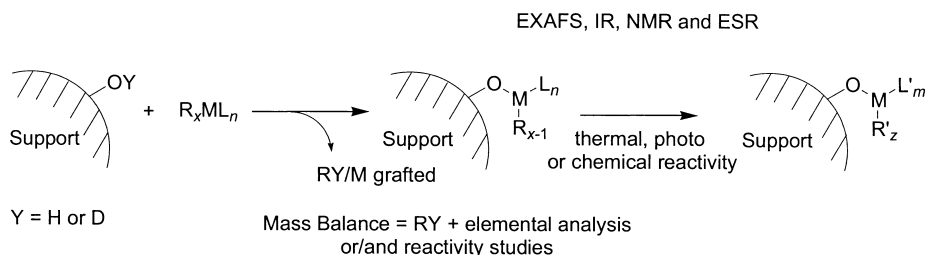
1.12.1

Introduction

Olefin metathesis was discovered using heterogeneous catalysts based on transition-metal oxides, mainly MoO_3 and WO_3 , supported on silica or alumina, which catalytically transformed propene into ethene and butenes [1, 2]. A major breakthrough was the subsequent discovery in the middle of the 1960s by British Petroleum that $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ could achieve this reaction at room temperature [3] and that functionalized olefins, (methyl oleate) could also be converted when co-catalysts (alkylating agents such as tetraalkyltin) were used [4]. Group 6 systems have been developed into industrial processes for non-functionalized olefins [1], but in 30 years no major breakthrough has appeared in heterogeneous catalysis, especially for functionalized olefins (see Section 1.12.3 for further comments). On the other hand, molecular organometallic chemistry has clearly demonstrated that metallocarbenes are the key intermediates [5] and has worked to generate well-defined systems of that type [6]. Now the latest generation of homogeneous catalysts display activity, selectivity, and tolerance to functional groups often unseen for their heterogeneous competitors (Scheme 1.12-1) [7]. Therefore, one might



Scheme 1.12-1. Examples of homogeneous olefin metathesis catalysts. R_F = $[(\text{CF}_3)_2(\text{CH}_3)\text{C}]$, R = Ph or $\text{CH}=\text{CMe}_2$, $\text{R}' = \text{CH}_2\text{tBu}$, Ar = Aryl substituent, and L_1/L_2 = tricyclohexylphosphine, triphenylphosphine or carbene ligands.



Scheme 1.12-2. General strategy to understand structures of surface complexes.

ask if it is possible to use the same strategy for heterogeneous catalysts, i.e., to generate well-defined metallocarbenes heterogenized on a support, but homogeneous in composition and distribution (ultimately a single site catalyst). Using this approach, it should be possible to draw structure-activity relationships so as to improve the catalytic systems rationally. We want to present here some of our latest results with this objective.

1.12.2

Preparation and Characterization of Well-Defined Metallocarbenes and Metallocarbynes via Surface Organometallic Chemistry

1.12.2.1

Strategy and Tools in Surface Organometallic Chemistry

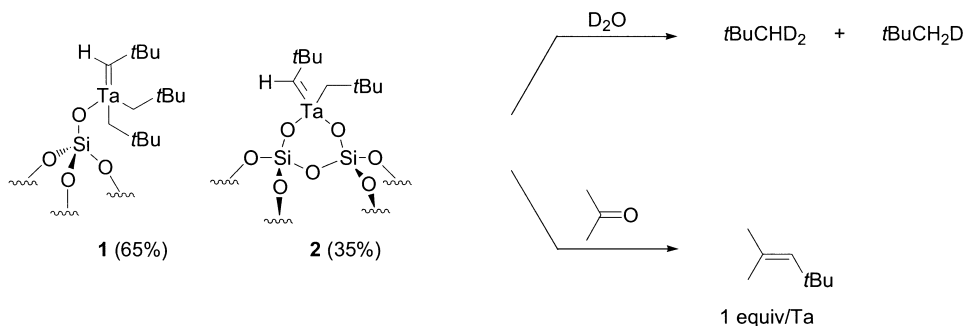
As in molecular chemistry, surface organometallic chemistry (SOMC) relies heavily on both chemical and spectroscopic methods to understand the structure of surface entities. SOMC concentrates first on understanding the interaction of the support and the organometallic precursor in order to find the proper reaction conditions to generate isolated well-defined metal centers surrounded by appropriate ligands (those that will provide high selectivity, activity, and lifetime in catalysis). The first step is to evaluate the reaction with the surface of the solid by using quantitative measurements of product evolution during grafting and, upon further chemical treatments of the surface complex, to establish a mass balance (Scheme 1.12-2). In a second step, SOMC relies heavily on spectroscopic methods such as EXAFS (which gives access to bond distances with the neighbors of the metal center and its average coordination numbers), IR (which allows us to follow modification of the support upon grafting or further treatment of the surface complex), ESR, and XANES (which can point out the oxidation state and the geometry of the metal complex), along with 1D and 2D solid-state NMR (a powerful method for structure determination) [8]. Additionally, molecular models, which mimic the surface of oxides such as polyoligomeric silsesquioxanes (POSS) [9], can also be of great help in understanding the reaction of an organometallic precursor with a surface (typically with silanols) and in helping to establish the molecular structure of a surface complex.

All these combined techniques help to build a molecular understanding of the chemical events and structures on a surface in order to establish key parameters to construct well-defined structures (*vide infra*) and to describe chemical entities on a surface at a molecular level, the so-called surface complex.

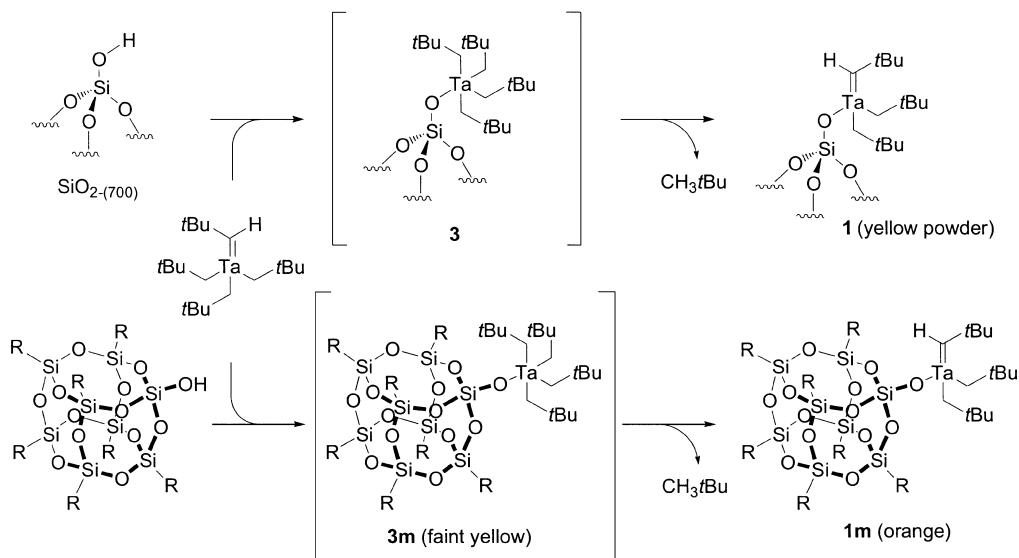
1.12.2.2

Application to the Preparation of Well-Defined Metallocarbene and Metallocarbyne Supported on Oxides

The first well-defined metal alkylidene system supported on silica was reported in 1995 (See Section 1.12.3.1 for further comments). It was prepared by contacting $[\text{Ta}(\text{=CH}t\text{Bu})(\text{CH}_2t\text{Bu})_3]$ with a silica partially dehydroxylated at 500 °C ($\text{SiO}_{2-(500)}$) (Scheme 1.12-3). After careful mass balance analysis and chemical reactivity studies, the surface was shown to be composed of a 65/35 mixture of mono-siloxy ($x = 1$, **1**) and bis(siloxy) ($x = 2$, **2**) surface complexes $[(\text{=SiO})_x\text{Ta}(\text{=CH}t\text{Bu})(\text{CH}_2t\text{Bu})_{3-x}]$ [10]. The presence of the alkylidene ligand was strongly suggested by both deuterolysis (formation of 1 equivalent of $t\text{BuCHD}_2/\text{Ta}$) and pseudo-Wittig reaction with acetone, which yielded 1 equivalent of $(t\text{BuCH}=\text{CMe}_2)/\text{Ta}$. In order to obtain a truly well-defined alkylidene system, the influence of the dehydroxylation temperature of silica on the proportion of the two surface complexes was investigated. Indeed, while lower temperatures of partial dehydroxylation, e.g., 200–300 °C, increase the density of surface silanols, higher temperatures allow us to decrease their density so as to obtain only isolated silanols on the surface [11]. Therefore, by using a $\text{SiO}_{2-(700)}$ it is possible to generate the monosiloxy complex **1** $[(\text{=SiO})\text{Ta}(\text{=CH}t\text{Bu})(\text{CH}_2t\text{Bu})_2]$ selectively (>95%; Scheme 1.12-4), and the bis(siloxy) complex **2**, $[(\text{=SiO})_2\text{Ta}(\text{=CH}t\text{Bu})(\text{CH}_2t\text{Bu})_2]$, is obtained as a major product (~90%) on a silica partially dehydroxylated at 300 °C [12]. In the case of **1**, partially ^{13}C -enriched on the α -position of the metal center $[\text{=SiO}-\text{Ta}(\text{=C}^*\text{H}t\text{Bu})\cdot(\text{C}^*\text{H}_2t\text{Bu})_2]$, 1D and 2D HETCOR solid-state NMR spectroscopies clearly point out the presence of neopentyl and neopentylidene ligands and confirm its structure [13]. EXAFS data on **1** are consistent with four neighboring atoms around the Ta center at 2.15 Å (2 Ta–C) and 1.87 Å (1 Ta–O + 1 Ta=C) [14]. The use of POSS



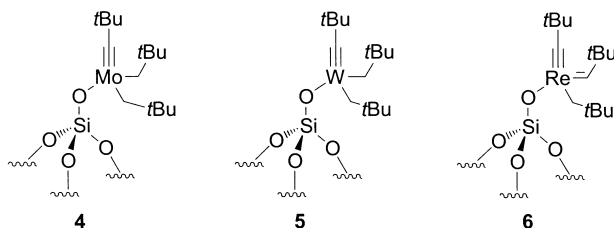
Scheme 1.12-3. Grafting of $[\text{Ta}(\text{=CH}t\text{Bu})(\text{CH}_2t\text{Bu})_3]$ with silica partially dehydroxylated at 500 °C.



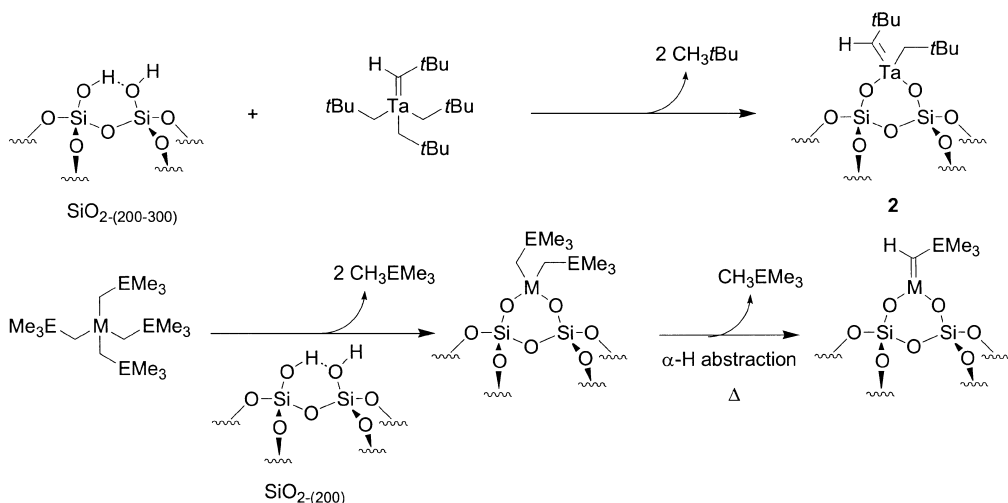
Scheme 1.12-4. Comparison of surface and molecular chemistry in the reaction of $[\text{Ta}(=\text{CHtBu})(\text{CH}_2\text{tBu})_3]$ with silica partially dehydroxylated at 700°C and a POSS ($\text{R} = o\text{-C}_5\text{H}_9$), a model for the silica surface.

analogues further corroborates these results by displaying ^1H and ^{13}C chemical shifts close to or identical to those of **1** [25]. Moreover, the use of this model reaction has allowed the observation of the reaction intermediate **3m**, namely, $[(\text{C}_5\text{H}_9)_7(\text{Si}_7\text{O}_{12})\text{SiO}-\text{Ta}(\text{CH}_2\text{tBu})_4]$, which arises from the addition of the silanol to the carbenic moiety of $[\text{Ta}(=\text{CHtBu})(\text{CH}_2\text{tBu})_3]$ and which slowly decomposes via $\alpha\text{-H}$ abstraction into **1m** $[(\text{C}_5\text{H}_9)_7(\text{Si}_7\text{O}_{12})\text{SiO}-\text{Ta}(=\text{CHtBu})(\text{CH}_2\text{tBu})_2]$, the molecular analogue of **1** (Scheme 1.12-4). The corresponding intermediate **3** was consecutively observed on the silica surface by solid-state NMR spectroscopy [13].

Transition metal complexes of group 6 and 7, namely, $[\text{M}(\equiv\text{CtBu})(\text{CH}_2\text{tBu})_3]$ ($\text{M} = \text{Mo}$ or W) and $[\text{Re}(\equiv\text{CtBu})(=\text{CHtBu})(\text{CH}_2\text{tBu})_2]$, react with $\text{SiO}_{2-(700)}$ to yield the corresponding well-defined monosiloxy surface complex according to gas evolution and elemental analysis, i.e., the evolution of one neopentane per grafted metal and the retention of the complementary ligands around the metal center (Scheme 1.12-5). Moreover, 1D and 2D HETCOR solid-state NMR along with EXAFS spectroscopies have been critical in determining the structure of the surface complexes due to the structure complexity of the starting molecular complexes. Using these techniques, the following surface complexes were prepared and fully characterized: $[\equiv\text{SiO}-\text{M}(\equiv\text{CtBu})(\text{CH}_2\text{tBu})_2]$ ($\text{M} = \text{Mo}$, **4** [15]; $\text{M} = \text{W}$, **5** [16]) and $[\equiv\text{SiO}-\text{Re}(\equiv\text{CtBu})(=\text{CHtBu})(\text{CH}_2\text{tBu})]$, **6** [17, 18]. One should note that the structure of the starting complex is retained, i.e., a neopentyl substituent has just been replaced by a siloxy group from the silica surface. On a $\text{SiO}_{2-(700)}$, silanols are sufficiently isolated to yield monosiloxy surface complexes, and silica behaves like a bulky $\eta\text{-1}$ solid ligand.

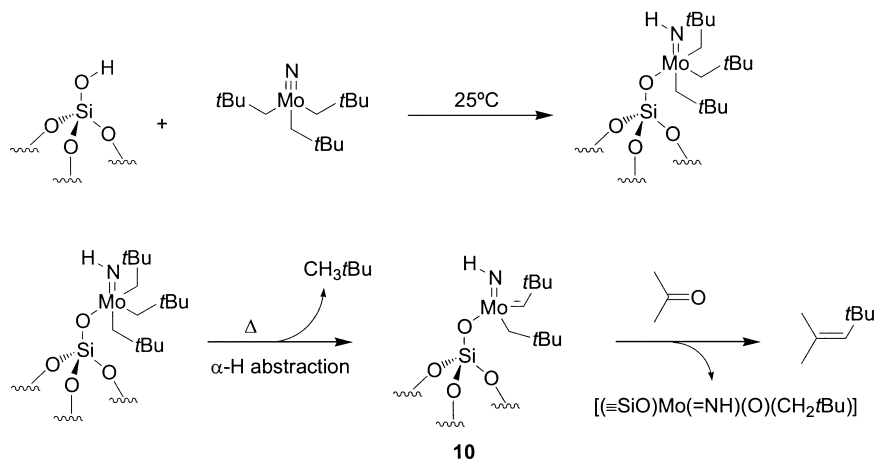


Scheme 1.12-5. Well-defined metallocarbenes and carbynes supported on silica.



Scheme 1.12-6. Grafting of $[\text{Ta}(=\text{CHtBu})(\text{CH}_2\text{tBu})_3]$ (top) and $[\text{M}(\text{CH}_2\text{EMe}_3)_4]$ ($\text{M} = \text{Ti}, \text{V}$ and Cr ; $\text{E} = \text{C}$ or Si ; bottom) on a silica partially dehydroxylated at 200 °C and subsequent thermolysis.

On the other hand, partial dehydroxylation of silica at lower temperatures, e.g. 200–300 °C, $\text{SiO}_{2-(200-300)}$, can allow us to generate selectively well-defined bis(siloxy) complexes according to mass balance analyses, as already mentioned for the grafting of $[\text{Ta}(=\text{CHtBu})(\text{CH}_2\text{tBu})_3]$ on a $\text{SiO}_{2-(200)}$ or (300), which generates the bis-(siloxy) surface complex $[(\equiv\text{SiO})_2\text{Ta}(=\text{CHtBu})(\text{CH}_2\text{tBu})]$ (**2**) (Scheme 1.12-6). Using this strategy, group 4–6 bis-(siloxy)bis(neopentyl) surface complexes such as $[(\equiv\text{SiO})_2\text{M}(\text{CH}_2\text{EMe}_3)_2]$ with Ti^{IV} ($\text{E} = \text{C}$), V^{IV} ($\text{E} = \text{Si}$) and Cr^{IV} ($\text{E} = \text{C}$ or Si , respectively) have been prepared and further converted into the corresponding alkylidene complexes by elimination of one neopentane upon thermolysis (Scheme 1.12-6: $[(\equiv\text{SiO})_2\text{M}(=\text{CHEMe}_3)]$, **7** ($\text{M} = \text{Ti}$ and $\text{E} = \text{C}$), **8** ($\text{M} = \text{V}$ and $\text{E} = \text{Si}$), **9a** and **9b** (for $\text{M} = \text{Cr}$ with $\text{E} = \text{C}$ and Si , respectively) [19, 20]. The aforementioned strategy to form alkylidene was previously used to generate a surface complex very close to the olefin metathesis catalysts developed by Schrock et al. [21]: $[\equiv\text{SiO}-\text{Mo}(=\text{NH})(=\text{CHtBu})(\text{CH}_2\text{tBu})]$ (**10**), that was prepared by the reaction of $[\text{Mo}(\equiv\text{N})(\text{CH}_2\text{tBu})_3]$ with silica ($\text{SiO}_{2-(500)}$ or $\text{SiO}_{2-(700)}$), to yield $[\equiv\text{SiO}-$



Scheme 1.12-7. Grafting of $[\text{Mo}(\text{N})(\text{CH}_2\text{tBu})_3]$ with silica partially dehydroxylated at 500 °C or 700 °C and subsequent thermolysis.

$\text{Mo}(=\text{NH})(\text{CH}_2\text{tBu})_3$. [22] A subsequent thermolysis at 70 °C gave **10** (Scheme 1.12-7). The presence of the alkylidene ligand was evidenced by the formation of 1 equivalent of 2,4,4-trimethyl-2-pentene via a pseudo-Wittig reaction between **10** and acetone [22a].

Moreover, the formation of carbenes can also be driven by the addition of PMe_3 to dialkyl surface complexes such as $[(\equiv\text{SiO})_2\text{Zr}(\text{CH}_2\text{tBu})_2]$ to form $[(\equiv\text{SiO})_2\text{Zr}(=\text{CHtBu})(\text{PMe}_3)]$ [23].

In conclusion, understanding the interaction of a support such as silica and organometallic complexes can allow us to obtain well-defined grafted metallocarbenes. The temperature of partial dehydroxylation can control the mode of grafting, and by a careful choice of this temperature, it is possible to generate either mono- or bis(grafted) surface species. In some cases similar studies have been carried out on other supports (alumina, nobia, etc.), but the corresponding surface species have been less defined (see below for further comments on these species).

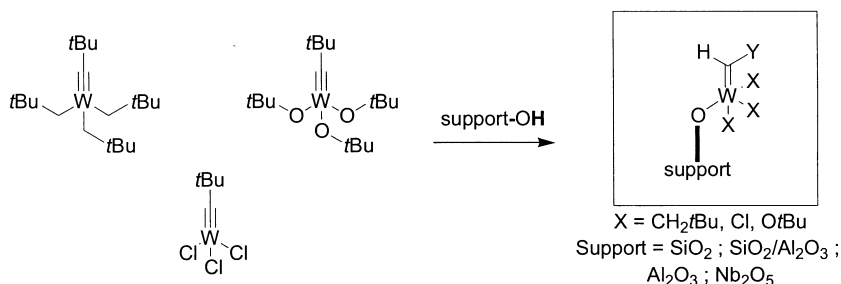
1.12.3

Reactivity in Alkene and Alkyne Metathesis

1.12.3.1

Group 5 and 6 Metallocarbenes and Metallocarbynes Supported on Oxides

The use of molecular organometallic compounds as precursors for the preparation of heterogeneous olefin metathesis catalysts was investigated very early [24]. The first reports involved the reaction of the group VI allyl derivatives $\{[\text{Mo}(\text{allyl})_4]$ or $[\text{W}(\text{allyl})_4]\}$ with oxide supports [25–27]; however, these materials are ill-defined,



Scheme 1.12-8. Attempts to generate well-defined metallocarbene supported on oxides from molecular metallocarbynes precursors.

and no structure-activity relationship could be readily drawn. Another approach used $\text{WMe}_6/\text{SiO}_2$ [28], which displayed good activities but suffered from the same problem of characterization. The first attempt to prepare a metallocarbene supported onto silica was undertaken by grafting $[\text{W}(\equiv\text{CtBu})(\text{OtBu})_3]$ onto a partially dehydroxylated silica (Scheme 1.12-8) [29]. While no direct spectroscopic evidence for the presence of the alkylidene ligand has been reported (in fact, see Section 1.12.2.2; grafting $[\text{W}(\equiv\text{CtBu})(\text{CH}_2\text{tBu})_3]$ generates a carbyne), the corresponding supported material displayed good activities in olefin metathesis (Table 1.12-1).

Tab. 1.12-1. Initial rates for the metathesis of propene with various heterogeneous catalysts.

Catalyst	TOF ^a (mol/mol/s)	Temp (°C)	R ^b	Ref.
$[\equiv\text{SiO-Ta}(\equiv\text{CHtBu})(\text{CH}_2\text{tBu})_2]$ 1	Inactive	25	1000	17b
$[\equiv\text{SiO-Mo}(\equiv\text{CtBu})(\text{CH}_2\text{tBu})_2]$ 4	0.53	25	500	17b
$[\equiv\text{SiO-W}(\equiv\text{CtBu})(\text{CH}_2\text{tBu})_2]$ 5	0.23	25	1700	17b
$[\equiv\text{SiO-Re}(\equiv\text{CtBu})(\equiv\text{CHtBu})(\text{CH}_2\text{tBu})]$ 6	0.25	25	500	15
$[\equiv\text{SiO-Mo}(\equiv\text{NH})(\equiv\text{CHtBu})(\text{CH}_2\text{tBu})]$ 7	0.47	25	830	21
$\text{Mo}(\text{allyl})_4/\text{SiO}_2$	0.17	90	— ^c	1
$\text{W}(\text{allyl})_4/\text{SiO}_2$	0.01–0.1	100	— ^c	1
$\text{W}(\equiv\text{CtBu})(\text{OtBu})_3/\text{SiO}_2$	>1.5	69	10 ^{4c}	27
$\text{WMe}_6/\text{SiO}_2$	— ^d	25	— ^c	26
$\text{MoO}_3/\text{SiO}_2$	0.004	400	— ^c	1
WO_3/SiO_2	— ^d	400	— ^c	1
$\text{Re}_2\text{O}_7/\text{SiO}_2$	<0.002	150	— ^c	40
$[\text{Re}(\text{CO})_3\text{OH}]_4/\text{SiO}_2$	0.00074	150	— ^c	40
$\text{MoO}_3/\text{Al}_2\text{O}_3$	0.05–0.5	200	— ^c	1
$\text{WO}_3/\text{Al}_2\text{O}_3$	0.1–1.0	300	— ^c	1
$\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$	0.05–0.1	25–35	— ^c	34b

^a Initial or steady state rates.

^b Substrate to catalyst ratio, for which the reaction reaches at least the thermodynamic equilibrium.

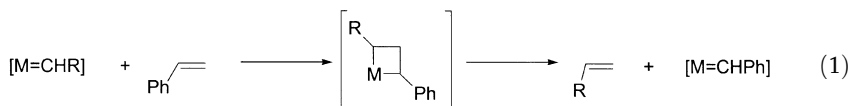
^c Not readily calculated from the published data.

^d Data obtained for the metathesis of 1-octene.

In this system the nature of the ligand around the metal, by grafting of various molecular precursors $[W(=CtBu)X_3]$ (for $X = Cl, OtBu$ and CH_2tBu), as well as the effect of the support have been investigated [30]. The support has a major influence, and typically $SiO_2-Al_2O_3 \sim Al_2O_3 \sim Nb_2O_5 > SiO_2$, which shows that Lewis acid sites accelerate the reaction, probably via the formation of cationic metal centers.

The first generation of fully characterized well-defined metallocarbenes is in fact relatively recent and corresponds to the formation of $[(\equiv SiO)Ta(=CHtBu)(CH_2tBu)_2]$ (Section 1.12.2). Nonetheless, this surface complex shows small activity in olefin metathesis (Table 1.12-1; see Section 1.12.4 for its application in alkane metathesis), which is not surprising for a tantalum complex [31].

Other metallocarbenes have been prepared as previously exemplified (see Section 1.12.2), and their reactivity towards olefins has been investigated. Contacting $[(\equiv SiO)_2M(=CHEMe_3)]$ ($M = V$ or Cr and $E = C$ or Si) with styrene gives $(tBuCH=CH_2)$ or $(Me_3SiCH=CH_2)$, which are probably formed via a cross-metathesis reaction between the respective alkylidene ligands and styrene (Eq. (1)). However, no further catalytic reactivity in olefin metathesis has been observed [32]. On the other hand, the Cr alkylidene surface complex, $[(\equiv SiO)_2Cr(=CHtBu)]$, has been reported to be quite active in ethylene polymerization and has been proposed as a model for the Philips catalyst [33].



One of the closest SOMC homologues of the Schrock catalyst is **10** $[(\equiv SiO)-Mo(=NH)(=CHtBu)(CH_2tBu)]$ [22]. This surface complex has high activity in olefin metathesis but still lower than that found for the corresponding homogeneous system, $[(R_F6O)_2Mo(=NAr)(=CHtBu)]$.

Group 6 well-defined metallocarbynes have also been prepared: $[\equiv SiO-M(=CtBu)(CH_2tBu)_2]$ ($M = Mo$, **4**; $M = W$, **5**), and their activity in olefin metathesis has been investigated. They display good activity in propene metathesis (Eq. (1)); however, the formation of the active species, a metallocarbene, is not clear. Interestingly, their molecular precursors (perhydrocarbyl) are completely inactive, and it is clear that the surface siloxy group has a great influence on the reactivity of grafted metals [34].

1.12.3.2

Group 7 Metallocarbenes and Metallocarbynes Supported on Oxides

Classical Re_2O_7/Al_2O_3 has brought considerable hope to the field of olefin metathesis because it requires low reaction temperatures (35–100 °C) and because it can be compatible with functional groups. However, some key problems have slowed its development [35]: the low number of active sites (difficulty in improving the system via a rational design) [36], the acidity of the support (side reactions) [37], and the deactivation of the catalyst (cost of regeneration). An advantage of the

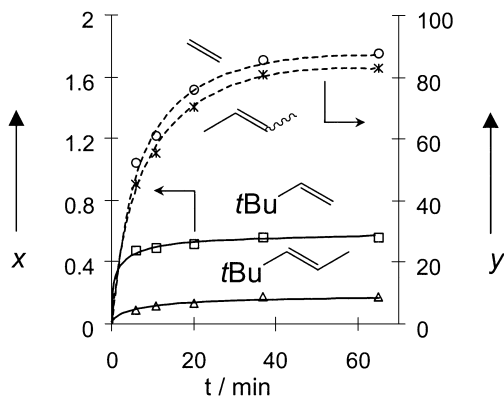


Fig. 1.12-1. Quantification in the gas phase of 3,3-dimethylbutene and *E* 4,4-dimethyl-2-pentene during propene metathesis (500 equivalents) catalyzed with **6** (1 equivalent) at 25 °C.

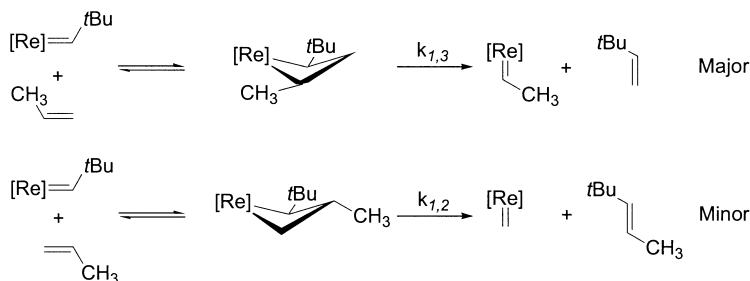
x = Cross-metathesis products in mol product.mol Re^{-1} .

y = Propene metathesis products in mol product.mol Re^{-1} .

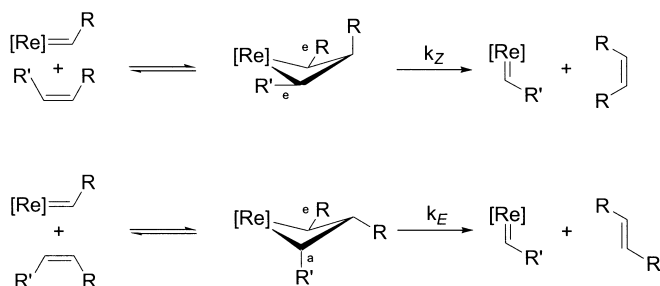
rhodium systems has been their activity in the metathesis of methyl oleate when alkyltin agents are used as activators [4]. Nonetheless, the turnover numbers are typically low, and these catalysts are not readily regenerated.

In the early 1990s, Herrmann et al. prepared a new generation of Re-based catalysts by using methyltrioxorhenium supported on silica-alumina ($\text{MeReO}_3/\text{SiO}_2\text{--Al}_2\text{O}_3$) [38]. These solids display high activity and are compatible with functional groups without the need of co-catalysts. In this system the initial carbene does not seem to originate from the methyl substituent of the organometallic precursor, MeReO_3 , and the initiation step is still a matter of debate [39]. Additionally, the acidity of the support is very important for this system, as for other rhenium-oxide-supported systems. Nb_2O_5 turned out to be the best support; for example, 500 equivalents of *cis*-2-pentene are converted into the equilibrated mixture in less than 5 min at room temperature (>1.3 mol/mol Re/s) [40]. It is in fact noteworthy that rhenium-oxide-based systems typically are not active when they are supported on silica [41].

In contrast, a well-defined silica-supported Re-alkylidene system $[(\text{=SiO})\text{Re}(\text{=C}t\text{Bu})(\text{=CH}t\text{Bu})(\text{CH}_2t\text{Bu})]$ has been reported recently to be a highly active olefin metathesis catalyst [17], even better than its Re-based homogeneous competitors [42]. This system readily catalyzes the metathesis of propene at room temperature (Eq. (2)) with an initial rate of 0.25 mol/(mol $\text{Re} \times \text{s}$). Noteworthy is the formation of about 1 equivalent of 3,3-dimethylbutene and 4,4-dimethylpentene in a 3-to-1 ratio, resulting from the cross-metathesis of propene and the neopentylidene ligand (Figure 1.12-1). Therefore, the initiation step is a simple cross-metathesis in sharp contrast to other heterogeneous catalysts for which it is not firmly identified. The ratio of the cross-metathesis products is in agreement with the expected



Scheme 1.12-9. Initiation step: cross-metathesis of propene and **6**.



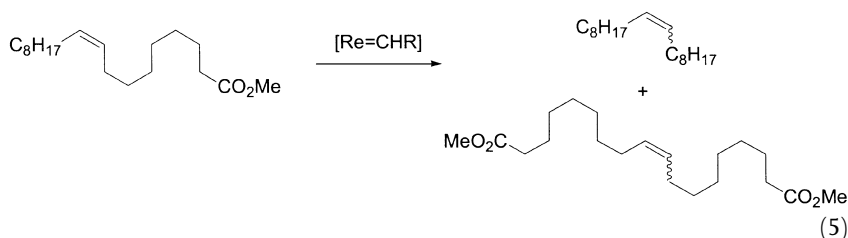
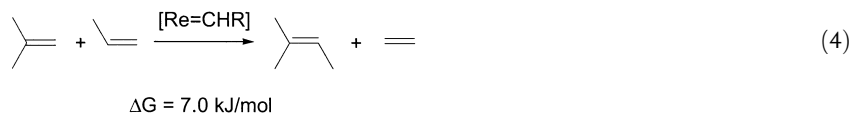
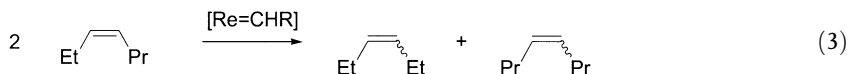
Scheme 1.12-10. Metathesis of *cis* 3-heptene.

relative stability of the metallacyclobutane intermediates (Scheme 1.12-9). The metathesis of *cis* 3-heptene is also noteworthy (Eq. (3)). For example, *cis* 3-heptene (1000 equivalents) is equilibrated in 8 h at 25 °C into a 1:1 mixture of 3-hexenes and 4-octenes, with an initial rate of 0.7 mol/mol Re/s, while *trans/cis* ratios for 3-hexenes and 4-octenes are 0.75 and 0.6, respectively, and are constant up to 45% conversion. The thermodynamic equilibrium is reached as conversion further proceeds (7:1 *trans/cis* ratio). This partial retention of configuration can be related to the relative stabilities of the metallacyclobutane intermediates, which is governed by [1,3]-interactions (Scheme 1.12-10) as initially proposed on various tungsten-based catalysts [43].



Moreover, cross-metathesis of propene and isobutene can readily be achieved (Eq. (4)), and this is the advantage of using silica, a neutral support in comparison to alumina, which catalyzes the oligomerization of isobutene [37]. Last but not least, this system catalyzes the self-metathesis of methyl oleate without the need of a co-catalyst (Eq. (5)). Turnover numbers of 900 can be reached, a value that is unprecedented for both heterogeneous and even for most homogeneous Re-based catalysts [44]. Finally, because the complex contains an alkylidyne moiety, it also

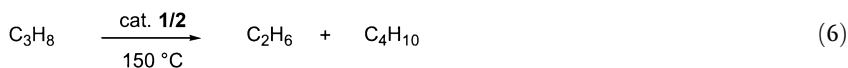
shows some catalytic activity in the metathesis of alkynes, such as 2-pentyne, like its closest homogeneous equivalent that also contains an alkylidyne ligand [45]. It shows the potential of these systems, and further development should probably appear in the literature within a short time.



1.12.4

Reactivity in Alkane Metathesis

More recently, the reactivity towards alkanes of $[(\equiv\text{SiO})_x\text{Ta}(\text{=CH}t\text{Bu})(\text{CH}_2t\text{Bu})_{3-x}]$, **1** ($x = 1$) and/or **2** ($x = 2$), has been investigated [46]. At 150 °C these surface complexes catalyze the transformation of alkanes into a mixture of their higher and lower homologues (Eq. (6)), with a reactivity similar to that observed for $[(\equiv\text{SiO})_2\text{Ta-H}]$ (Table 1.12-2) [47]. This reaction has been named alkane σ -bond metathesis because alkyl fragments of alkanes are exchanged like alkylidene fragments in the well-known alkene metathesis. In addition to self-metathesis products, neopentyl-containing alkanes were detected as a clear evidence for a cross-metathesis reaction between the neopentyl/neopentylidene ligands and the incoming alkanes (Table 1.12-2). The cross-metathesis between the metal-carbon bond and the incoming alkane follows a trend as depicted in Scheme 1.12-11, and C-H activation (alkyl exchange process) is about three times faster than C-C activation. After the discovery of the reaction with the highly electrophilic complex $[(\equiv\text{SiO})_2\text{Ta-H}]$, a Ta^{III} species, the reactivity of **1** and **2**, which are Ta^{V} species, implies that both are precursors to the same active species, perhaps in a +5 oxidation state. Mechanistic investigations on this reaction are still in progress.



Tab. 1.12-2. Stoichiometric cross-metathesis of alkanes with silica-supported tantalum complexes [1+2]. Selectivity in neopentyl-containing compounds and catalytic activity in alkane metathesis.

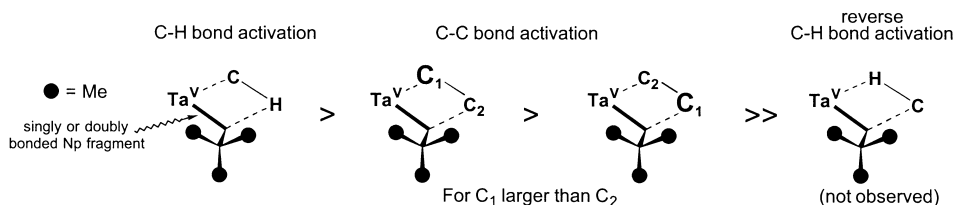
Entry	Alkane	$t\text{BuCH}_2\text{-H}$	$t\text{BuCH}_2\text{-Me}$	$t\text{BuCH}_2\text{-Et}$	$t\text{BuCH}_2\text{-Pr}$	$t\text{BuCH}_2\text{-iPr}$	Total amount of $t\text{BuCH}_2\text{-X}$ in the gas phase ^a	TON ^b
1	Ethane	76	24	<1 ^c	— ^d	— ^d	37%	25(46)
2	Propane	70	26	4	<1 ^c	— ^d	48%	58(60)
3	Butane	70	15	11	3	— ^d	48%	55(55)
4	Isobutane	71	29	— ^d	— ^d	<1 ^c	51%	33(40)

^ayield with the respect to the amount of $(\text{CH}_2t\text{Bu} + =\text{CH}t\text{Bu})$ on the surface before reaction.

^bTON is defined as the number of rotations. The numbers in parenthesis correspond to those in the case of $[(=\text{SiO})_2\text{Ta-H}]$.

^cThese compounds were detected in about 0.1% after concentration of the gas phase.

^dNot detected (<0.1% if any).



Scheme 1.12-11. Order of reactivity of alkanes with **1** or **2**, $[(=\text{SiO})_x\text{Ta}(=\text{CH}t\text{Bu})(\text{CH}_2t\text{Bu})_{3-x}]$.

1.12.5

Summary and Outlook

To conclude, it appears that a new generation of well-defined olefin metathesis catalysts can be prepared via SOMC. These catalysts are based on supported metallocarbenes or carbynes of Mo, W, or Re. They exhibit activities, selectivities, and lifetimes close, and in some cases superior, to those encountered in classical heterogeneous and even homogeneous catalysis. The SOMC strategy has now reached a level of reliability that allows us to achieve a real structure-activity relationship in heterogeneous catalysis and that allows the improvement of activity, selectivity, lifetime, and regeneration of heterogeneous catalysts in a rational way, even if the use of these systems in industry is still a matter of choice between ease and cost of preparation and gain of performances.

Surface organometallic chemistry can also generate entities that display reactivities never observed in either heterogeneous or homogeneous catalysis. This difference is probably due to the high electrophilicity of these surface complexes in combination with a stabilization by the surface of reactive intermediates (no pos-

sibility of dimerization). This has allowed us to discover highly active catalysts and a new reaction: alkane metathesis.

Acknowledgments

The authors gratefully acknowledge the contributions of the many co-workers involved in these projects, whose names are listed within the references, with a special thanks to A. Lesage, S. Hediger, and L. Emsley for their collaboration on the development of solid-state NMR spectroscopy applied to our problems. We are also very grateful to Y. Chauvin for many helpful discussions. This work was made possible by the support of the CNRS, ESCPE Lyon, La Région Rhône-Alpes, The French Ministry for Research and Technology (MENRT), and all our past and present industrial partners.

References

- 1 In *Olefin Metathesis and Metathesis Polymerization* (Eds. K. J. IVIN, J. C. MOL), Academic Press, **1997**.
- 2 a) H. S. EULETERIO, US Patent, 3074918, **1963**. b) R. L. BANKS, G. C. BAILEY, *Ind. Eng. Chem., Prod. Res. Div.* **1964**, 3, 170.
- 3 a) NL Patent, 6605328, **1966**. b) For a review on this system, see: J. C. MOL, *Catalysis Today* **1999**, 51, 289.
- 4 a) E. VERKUIJLEN, F. KAPTEIJN, J. C. MOL, C. BOELHOUWER, *J. Chem. Soc., Chem. Commun.* **1977**, 198. b) M. SIBEIJN, J. C. MOL, *Appl. Catal.* **1991**, 67, 279.
- 5 J.-L. HÉRISSON, Y. CHAUVIN, *Makromol. Chem.* **1970**, 141, 161.
- 6 R. R. SCHROCK, *Chem. Rev.* **2002**, 102, 145.
- 7 Review on olefin metathesis for homogeneous catalysis. a) R. H. GRUBBS, *Acc. Chem. Res.* **2001**, 34, 18. b) R. R. SCHROCK, A. H. HOVEYDA, *Chem. Eur. J.* **2001**, 7, 945.
- 8 C. COPÉRET, M. CHABANAS, R. PETROFF SAINT-ARROMAN, J.-M. BASSET, *Angew. Chem. Int. Ed.* **2003**, 42, 156.
- 9 a) F. J. FEHER, T. A. BUDZICHOWSKI, *Polyhedron* **1995**, 14, 3239. b) P. T. WOLCZANSKI, *Polyhedron* **1995**, 14, 3335. c) P. D. LICKISS, *Adv. Inorg. Chem.* **1995**, 42, 147. d) R. MURUGAVEL, A. VOIGT, M. G. WALAWALKAR, H. W. ROESKY, *Chem. Rev.* **1996**, 96, 2205. e) P. G. HARRISON, *J. Organomet. Chem.* **1997**, 542, 141. f) L. KING, A. C. SULLIVAN, *Coord. Chem. Rev.* **1999**, 189, 19. g) V. LORENZ, A. FISCHER, S. GIESSMANN, J. W. GILJE, Y. GUN'KO, K. JACOB, F. T. EDELMANN, *Coord. Chem. Rev.* **2000**, 206–207, 321. h) H. C. L. ABBENHUIS, *Chem. Eur. J.* **2000**, 6, 25. i) B. MARCINIEC, H. MACIEJEWSKI, *Coord. Chem. Rev.* **2001**, 223, 301.
- 10 V. DUFUD, G. P. NICCOLAI, J. THIVOLLE-CAZAT, J.-M. BASSET, *J. Am. Chem. Soc.* **1995**, 117, 4288.
- 11 a) In *Studies in Surface Science and Catalysis*, (Eds. E. F. VANSANT, P. VAN DER VOORT, K. C. VRANCHEN), Elsevier, Vol. 93, **1995**. (b) In *The Surface Properties of Silica*, (Ed.: A. P. LEGRAND), Wiley, **1998**.
- 12 L. LEFORT, M. CHABANAS, O. MAURY, D. MEUNIER, C. COPÉRET, J. THIVOLLE-CAZAT, J.-M. BASSET, *J. Organometal. Chem.* **2000**, 593–594, 96.
- 13 M. CHABANAS, A. E. QUADRELLI, C. COPÉRET, J. THIVOLLE-CAZAT, J.-M. BASSET, A. LESAGE, L. EMSLEY, *Angew. Chem.* **2001**, 113, 4625; *Angew. Chem. Int. Ed.* **2001**, 43, 4493.
- 14 M. CHABANAS, W. LUKENS, C. COPÉRET, J.-M. BASSET, unpublished results.
- 15 R. PETROFF SAINT-ARROMAN, M. CHABANAS, C. COPÉRET, J.-M. BASSET, L. EMSLEY, *J. Am. Chem. Soc.* **2001**, 123, 3820.

- 16 M. CHABANAS, D. ALCOR, E. GAUTIER, C. COPÉRET, J.-M. BASSET, A. LESAGE, S. HEDIGER, L. EMSLEY, W. LUKENS, manuscript in preparation.
- 17 M. CHABANAS, A. BAUDOUIN, C. COPÉRET, J.-M. BASSET, *J. Am. Chem. Soc.* **2001**, 123, 2062.
- 18 a) M. CHABANAS, A. BAUDOUIN, C. COPÉRET, J.-M. BASSET, W. LUKENS, A. LESAGE, S. HEDIGER, L. EMSLEY, *J. Am. Chem. Soc.* **2003**, 125, 492. M. CHABANAS, C. COPÉRET, J.-M. BASSET, S. HEDIGER, A. LESAGE, L. EMSLEY, manuscript in preparation. b) M. CHABANAS, PhD Thesis, Université Claude Bernard Lyon I, **2001**.
- 19 J. AMOR NAIT AJJOU, S. L. SCOTT, V. PAQUET, *J. Am. Chem. Soc.* **1998**, 120, 415.
- 20 J. AMOR NAIT AJJOU, G. L. RICE, S. L. SCOTT, *J. Am. Chem. Soc.* **1998**, 120, 13436.
- 21 a) R. R. SCHROCK, *Acc. Chem. Res.* **1990**, 23, 158. b) J. FELDMAN, R. R. SCHROCK, *Prog. Inorg. Chem.* **1991**, 39, 1. c) R. R. SCHROCK, *Polyhedron* **1995**, 14, 3177. d) R. R. SCHROCK, *Top. Organomet. Chem.* **1998**, 1.
- 22 a) W. A. HERRMANN, A. W. STUMPF, T. PRIERMEIER, S. BOGDANOVIC, V. DUFAUD, J.-M. BASSET, *Angew. Chem.* **1996**, 108, 2978; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2803. b) Q. YANG, C. COPÉRET, J.-M. BASSET, unpublished results.
- 23 V. RIOLLET, Master Thesis, Université Claude Bernard Lyon I, **1999**.
- 24 C. COPÉRET, J. THIVOLLE-CAZAT, J.-M. BASSET, In *Fine Chemicals through Heterogeneous Catalysis*, (Eds.: R. A. SHELDON, H. VAN BEKKUM), Wiley-VCH, Weinheim, **2001**, p. 553.
- 25 A. ORESHKIN, L. I. RED'KINA, K. L. MAKOVETSKII, E. I. TINYAKOVA, B. A. DOLGOPLOSK, *Izv. Akad. Nauk S.S.S.R., Ser. Khim.*, **1971**, 5, 1123.
- 26 Y. I. YERMAKOV, B. N. KUZNETSOV, Y. A. RYNDIN, *J. Catal.* **1976**, 42, 73.
- 27 Y. IWASAWA, Y. NAKANO, S. OGASAWARA, *J. Chem. Soc., Faraday I*, **1978**, 74, 2968.
- 28 a) W. MOWAT, J. SMITH, D. A. WHAN, *J. Chem. Soc., Chem. Commun.* **1974**, 34. b) J. SMITH, W. MOWAT, D. A. WHAN, E. A. V. EBSWORTH, *J. Chem. Soc., Dalton Trans.* **1974**, 1742.
- 29 K. WEISS, G. LOESSEL, *Angew. Chem.* **1989**, 101, 75; *Angew. Chem. Int. Ed.* **1989**, 28, 62.
- 30 R. BUFFON, M. LECONTE, A. CHOPLIN, J.-M. BASSET, *J. Chem. Soc., Chem. Commun.*, **1993**, 361. b) R. BUFFON, M. LECONTE, A. CHOPLIN, J.-M. BASSET, *J. Chem. Soc., Dalton Trans.* **1994**, 1723.
- 31 S. M. ROCKLAGE, J. D. FELLMANN, G. A. RUPPRECHT, L. W. MESSERLE, R. R. SCHROCK, *J. Am. Chem. Soc.* **1981**, 103, 1440.
- 32 M. C. BEAUDOIN, O. WOMILOJU, A. FU, J. A. N. AJJOUR, G. L. RICE, S. L. SCOTT, *J. Mol. Cat.* **2002**, in press.
- 33 a) J. AMOR NAIT AJJOU, S. L. SCOTT, *J. Am. Chem. Soc.* **2000**, 122, 8968. b) J. AMOR NAIT AJJOU, *Chem. Eng. Science* **2001**, 56, 4155.
- 34 D. G. H. BALLARD, *Adv. Catal.* **1973**, 23, 263.
- 35 J. COSYNS, J. CHODORGE, D. COMMEREUC, B. TORCK, *Hydrocarbon Process* **1998**, 60.
- 36 F. KAPTEIJN, H. L. G. BREDT, E. HOMBURG, J. C. MOL, *Ind. Eng. Chem., Prog. Res. Dev.* **1981**, 20, 457. b) Y. CHAUVIN, D. COMMEREUC, *J. Chem. Soc., Chem. Commun.*, **1992**, 462.
- 37 a) NAKAMURA, H. IIDA, E. ECHIGOYA, *Chem. Lett.* **1972**, 273. b) W. VON SIEGFRIED, G. PUETZ, *Chem.-Ztg.* **1988**, 15.
- 38 W. A. HERRMANN, W. WAGNER, U. N. FLESSNER, U. VOLKHARDT, H. KOMBER, *Angew. Chem. Int. Ed.* **1991**, 30, 1636.
- 39 a) R. BUFFON, A. CHOPLIN, M. LECONTE, J.-M. BASSET, R. TOUROUDE, W. A. HERRMANN, *J. Mol. Cat.* **1992**, 72, L7–10. b) L. J. MORRIS, A. J. DOWNS, T. M. GREENE, G. S. McGRADY, W. A. HERRMANN, P. SIRSCH, O. GROPEN, W. SCHERER, *Chem. Commun.* **2000**, 67. c) L. J. MORRIS, A. J. DOWNS, T. M. GREENE, G. S. McGRADY, W. A. HERRMANN, P. SIRSCH, W. SCHERER, O. GROPEN, *Organometallics* **2001**, 20, 2344.
- 40 R. BUFFON, A. AUROUX, F. LEFEBVRE, M. LECONTE, A. CHOPLIN, J.-M. BASSET, W. A. HERRMANN, *J. Mol. Cat.* **1992**, 76, 287–295.

- 41 The activity of rhenium oxides supported on silica is usually poor under 120 °C. a) A. W. ALDAG, C. J. LIN, A. CLARK, *Rec. Trav. Chim. Pays-Bas*, **1977**, 96, M27. b) N. TSUDA, A. FUJIMORI, *J. Catal.* **1981**, 69, 410. c) L. G. DUQUETTE, R. C. CIESLINSKI, C. W. JUNG, P. E. GARROU, *J. Catal.* **1984**, 90, 362. d) P. S. KIRLIN, B. C. GATES, *J. Chem. Soc., Chem. Comm.*, **1985**, 277. e) R. M. EDREVA-KARDJIEVA, A. A. ANDREEV, *J. Catal.* **1986**, 97, 321.
- 42 a) R. TOREKI, G. A. VAUGHAN, R. R. SCHROCK, W. M. DAVIS, *J. Am. Chem. Soc.* **1993**, 115, 127; b) A. M. LAPOINTE, R. R. SCHROCK, *Organo-metallics*, **1995**, 14, 1875; c) B. T. FLATT, R. H. GRUBBS, R. L. BLANSKI, J. C. CALABRESE, J. FELDMAN, *Organo-metallics*, **1994**, 13, 2728; d) D. COMMEREUC, *J. Chem. Soc., Chem. Comm.*, **1995**, 791.
- 43 a) J. L. BILHOU, J.-M. BASSET, R. MUTIN, W. F. GRAYDON, *J. Chem. Soc., Chem. Commun.* **1976**, 23, 970. b) J. L. BILHOU, J.-M. BASSET, R. MUTIN, W. F. GRAYDON, *J. Am. Chem. Soc.* **1977**, 99, 4083.
- 44 M. CHABANAS, C. COPÉRET, J.-M. BASSET, *Chem. Eur. J.* **2003**, 9, 971.
- 45 A. WEINSTOCK, R. R. SCHROCK, W. M. DAVIS, *J. Am. Chem. Soc.* **1991**, 113, 135.
- 46 C. COPÉRET, O. MAURY, J. THIVOLLE-CAZAT, J.-M. BASSET, *Angew. Chem.* **2001**, 113, 2393; *Angew. Chem. Int. Ed.* **2001**, 40, 2331.
- 47 a) V. VIDAL, A. THÉOLIER, J. THIVOLLE-CAZAT, J.-M. BASSET, *Science* **1997**, 276, 99. b) O. MAURY, L. LEFORT, V. VIDAL, J. THIVOLLE-CAZAT, J.-M. BASSET, *Angew. Chem. Int. Ed.* **1999**, 38, 1952; *Angew. Chem.* **1999**, 111, 2121.

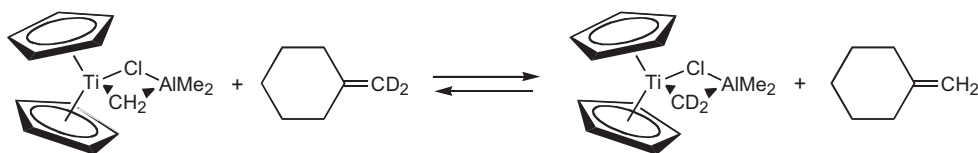
2.1

Olefin Metathesis and Related Reactions in Organic Synthesis: Introduction to Metal-Carbon Double Bonds in Organic Synthesis

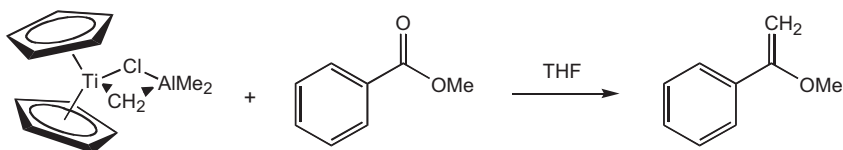
Robert H. Grubbs

Compounds containing metal-carbon double bonds have been explored extensively as reagents and catalysts in organic synthesis. As will be discussed in another section of this book, metal-carbon double bonds exhibit a wide range of reactivities. For example, low-valent metal carbonyl complexes – containing a carbene ligand – tend to react at the carbon atom of the carbene group with nucleophiles. These types of complexes, referred to as Fischer carbenes, were the first of this broad family to be discovered and explored [1]. The organic chemistry of these complexes has been reviewed extensively and, therefore, will not form part of the following discussions [2]. In the following chapters, the major emphasis will be placed on those higher oxidation state early metal complexes, those that typically react with electrophiles at the carbon atom and with later metal complexes that are involved in metathesis reactions.

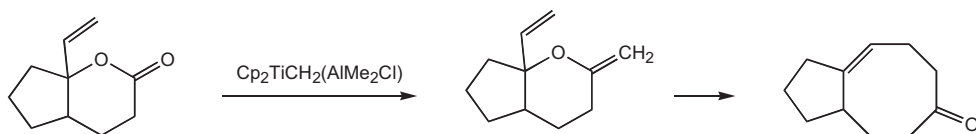
In 1978 Fred Tebbe was exploring the complex that had been isolated by Sinn from the reaction of trimethylaluminum with titanocene dichloride [3]. The structure of this complex is best represented as a titanium methylene complex that is stabilized via an interaction with dimethylaluminum chloride. Tebbe demonstrated that this complex would react with labeled olefins to give an olefin metathesis product [4].



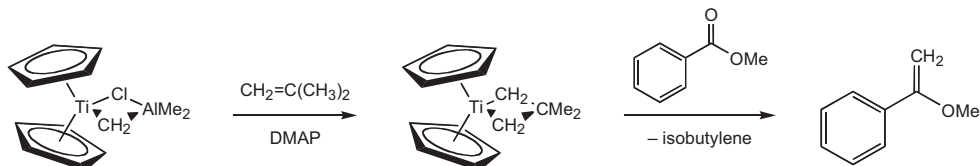
A footnote in the first paper reported that the complex reacted with ethyl acetate to produce the corresponding vinyl ether. This reaction, when combined with the observations by Schrock on tantalum alkylidene complexes [5], suggested that these species might have applications in organic chemistry. At the time, Professor Stan Pine was on sabbatical in my group at Caltech, and he, in collaboration with the Evans group, explored the use of this complex as a general route for the formation of vinyl ethers. Key to the application of this reagent, however, was the use of mild bases to complex the released alkylaluminum [6].



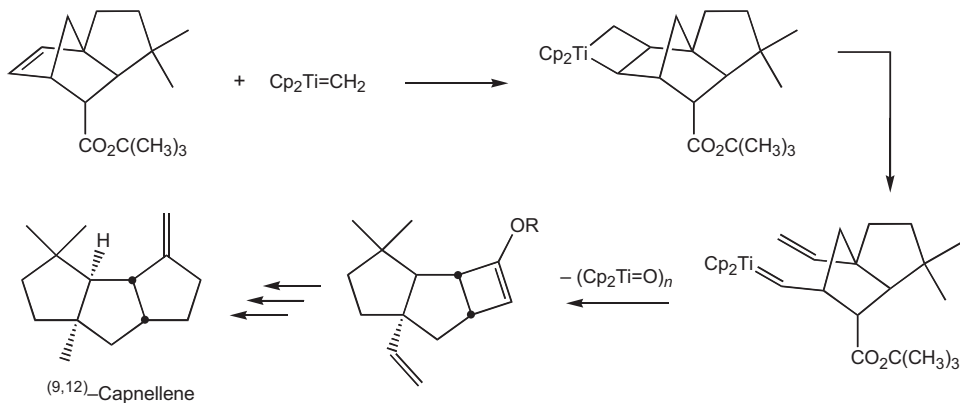
Indeed, this complex provided a general route for the synthesis of vinyl ethers from the corresponding esters, as well as a route for the conversion of base-sensitive ketones into the corresponding methylenes [7]. Straightforward routes for the synthesis of the Tebbe complex, combined with the results outlined above, opened up this approach as a general synthetic method in organic synthesis. For example, this reaction provides a facile route to starting materials for the Claisen-Ireland reaction [8].



It was also found that titanium metallacycles could be formed when the Tebbe reagent was allowed to react with olefins in the presence of strong bases. Once isolated, these complexes would thermally decompose to produce an intermediate titanium methylene complex that could be trapped by carbonyl compounds [9].

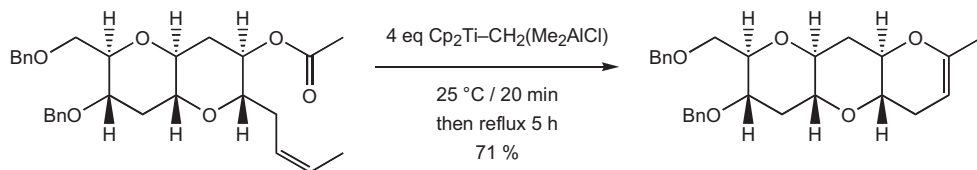


These two reactions, the formation and cleavage of metallacycles, and the olefination of carbonyl compounds were combined in a rapid synthesis of $\Delta^{9(12)}$ -capnellene [10].



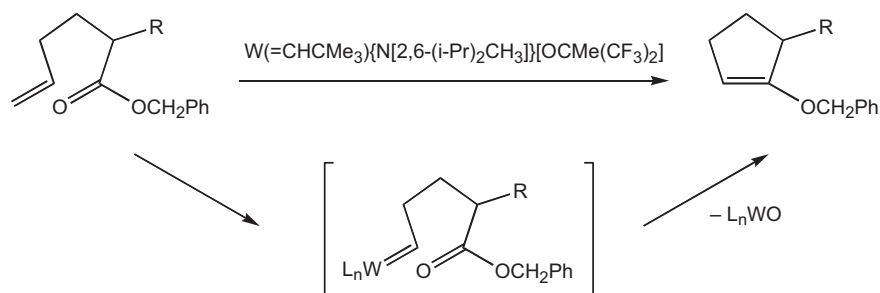
Dimethyltitanocene, a less air- and moisture-sensitive reagent that apparently generates the same titanium methylene intermediate as the Tebbe reagent, was introduced by Petasis in 1996 [11]. At higher temperatures the dimethyltitanocene eliminates methane to generate the reactive methylene intermediate. This reagent has been substituted for the Tebbe reagent in a number of applications [12].

If a large excess of the reagent is used at higher temperatures, olefin metathesis can be observed. Nicolaou found that the use of an excess of Tebbe reagent would perform both a methylenation and a ring-closing reaction.



This reaction apparently proceeds by the methylenation of the ester followed by formation of the metallacycle that subsequently cleaves to afford a titanium alkylidene that then undergoes ring closure [13]. The Nicolaou group has used this reaction for the synthesis of a number of polycyclic ethers [14].

Other alkylidene complexes will induce similar stoichiometric $\text{C}=\text{O}/\text{C}=\text{C}$ metathesis reactions. For example, it was found that some tungsten alkylidenes would undergo olefin metathesis more rapidly than the corresponding reaction with an ester carbonyl. This allows for the efficient ring closing of unsaturated esters to afford cyclic vinyl ethers [15].



The increased selectivity of related molybdenum complexes allows for similar cyclization of unsaturated ketones.

As more and more complexes were discovered that would (1) catalyze the olefin metathesis reaction and (2) would not react with common functional groups, the use of metal alkylidenes in organic synthesis began to focus on their catalytic applications in ring-closing metathesis and cross-metathesis reactions, as well as procedures that combine these transformations in one sequence. The following chapters examine the utility of these catalysts in a variety of applications in organic synthesis and have been written in a manner that stresses the topic of application.

As a result, a number of reactions and observations will be present in multiple chapters, with the emphasis shifting to different aspects of the reactions. There are two types of chapters. A majority of the chapters are planned to provide comprehensive coverage of a particular topic, whereas others are more personalized vignettes that focus on the research efforts of one person. Although this combination of styles may result in some duplication of information, it is hoped that this approach will provide a more personalized view of the field.

References

- 1 FISCHER, E. O.; KREISSL, F. R. J. *Organomet. Chem.* **1972**, *35*, C45–C51.
- 2 DEMEIJERE, A. *Pure Appl. Chem.* **1996**, *68*, 61–72. WULFF, W. D. In *Comprehensive Organic Synthesis*, Eds.: TROST, B. M.; FLEMING, I.; PAQUETTE, L. A., Pergamon Press Oxford, 1991, vol. 5, pp. 1065.
- 3 TEBBE, F. N.; PARSHALL, G. W.; REDDY, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.
- 4 TEBBE, F. N.; PARSHALL, G. W.; OVENALL, D. W. *J. Am. Chem. Soc.* **1979**, *101*, 5074–5075.
- 5 SCHROCK, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796–6797.
- 6 PINE, S. H.; ZAHLER, R.; EVANS, D. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272.
- 7 BROWN-WENSLEY, K. A.; BUCHWALD, S. L.; CANNIZZO, L.; CLAWSON, L.; HO, S.; MEINHARDT, D.; STILLE, J. R.; STRAUS, D.; GRUBBS, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733–1744.
- 8 IRELAND, R. E.; VARNEY, M. D. *J. Org. Chem.* **1983**, *48*, 1829–1833.
- 9 HOWARD, T. R.; LEE, J. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876–6878.
- 10 STILLE, J. R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855–856.
- 11 PETASIS, N. A.; LU, S.-P.; BZOWEJ, E. I.; FU, D.-K.; STASZEWSKI, J. P.; ADRIPOPOULOU-ZANZE, I.; PATANE, M. A.; HU, Y.-H. *Pure Appl. Chem.* **1996**, *68*, 667–670.
- 12 PETASIS, N. A.; HU, Y.-H. *Curr. Org. Chem.* **1997**, *1*, 249–286.
- 13 NICOLAOU, K. C.; POSTEMA, M. H. D.; CLAIRBORNE, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566.
- 14 NICOLAOU, K. C.; POSTEMA, M. H. D.; YUE, E. W.; NADIN, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335–10336.
- 15 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800–3801.

2.2

General Ring-Closing Metathesis

So-Yeop Han and Sukbok Chang

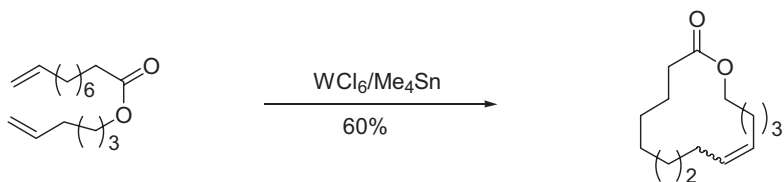
2.2.1

Introduction

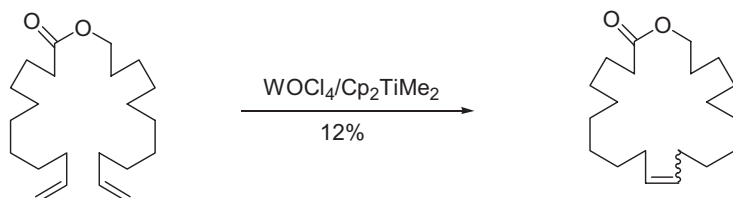
Olefin metathesis has grown to become one of the most important tools for organic chemists for the formation of C–C bonds. One of the most intriguing aspects of olefin metathesis is that several different types of chemistry can be performed with the same carbene catalysts depending on the reaction conditions and on the structural features of the substrates [1–3]. Early examples of ring-closing metathesis (RCM) reactions were reported for the first time by Villemin [4] and Tsuji [5] almost simultaneously. While diolefinic esters were cyclized with modest efficiency into macrocyclic lactones with co-catalyst systems of $\text{WCl}_6/\text{Me}_4\text{Sn}$, intramolecular metathesis reaction of dialkenyl ketone was unsuccessful with W–Ti catalytic systems (Scheme 2.2-1). This clearly demonstrated that the intramolecular metathesis yielded very useful products, which would be accessible only by way of several steps if traditional chemistry were applied. However, it also illustrated the high sensitivity of the catalytic system to the subtle changes of functional groups.

With the advent of well-defined carbene complexes for olefin metathesis reactions, this field of chemistry is now accepted as one of the most efficient methods for C–C bond generation. One of the most significant aspects in evaluating the carbene catalysts is compatibility for various functional groups as well as their high activities for metathesis reactions. From this aspect, Schrock's molybdenum-carbene complex **1** [6] and a series of Grubbs-type ruthenium carbenes, **2–5**, [7–10] provide sufficient activity and selectivity for the organic chemists (Figure 2.2-1).

In recent years, the area of ring-closing metathesis reactions has been considered as the most recognized field of olefin metathesis. There are several key aspects to the success of RCM as a tool for organic chemists: (1) the availability of efficient molybdenum and ruthenium pre-catalysts having sufficiently well-defined electronic and coordinative unsaturation to allow convenient use and high turnover performance; (2) the exceptional tolerance of these initiators to diverse functional groups, including the capacity of the Lewis-acidic metal-carbene centers to engage in intramolecular coordination to polar substituents in order to maximize proper



Villemin *TL* **1980**, 21, 1715



Tsuji *TL* **1980**, 21, 2955

Scheme 2.2-1

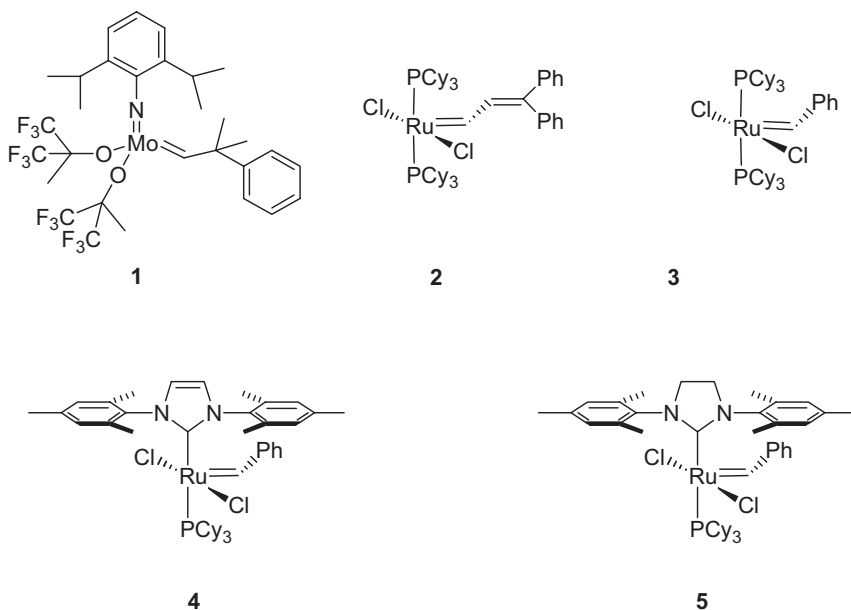


Fig. 2.2-1. Molybdenum- and ruthenium-carbene catalysts.

orientation of the reacting centers; and (3) one's ability to profit from the gain in entropy that drives the macrocyclization by ensuring that ethylene is the volatile byproduct.

The key competing reaction in RCM is the oligomerization as shown in Figure 2.2-2. The ratio of desired cyclic products to oligomers is determined by the

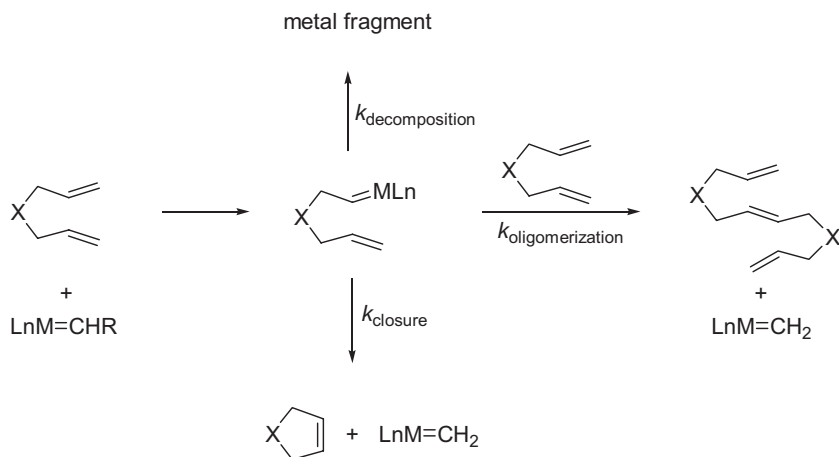


Fig. 2.2-2. Competing reactions between ring-closing metathesis and oligomerization.

ratio of $k_{\text{clo}}/(k_{\text{oligo}}[\text{diolefin}])$. As the rate of closure decreases due to ring size and conformational effects, the competing reactions interfere with the desired reaction. The rate of oligomerization, which is nearly a constant for specific olefin substitution, can be decreased by lowering the concentration of the diene or by using slow addition of the substrates. Higher temperature also favors ring closure. However, both of these factors, low concentrations and high temperature, which favor closure, also allow catalyst decomposition to start to compete with the desired reaction. As a result, closure of larger rings usually requires higher catalyst loading.

RCM is recognized as one of the most straightforward and reliable methods for the formation of small-, medium-, and large-ring systems and now compares favorably with all existing synthetic alternatives. Although there are numerous reviews on the metathesis chemistry by Grubbs [11–13] and others [14–23], it has become a tremendously difficult task to comprehensively review all the reported applications of RCM. In this book, we are trying to cover the work having important aspects either in concepts or in terms of application. The reaction has become so common that many RCM reactions are imbedded in a long total synthesis and are difficult to identify.

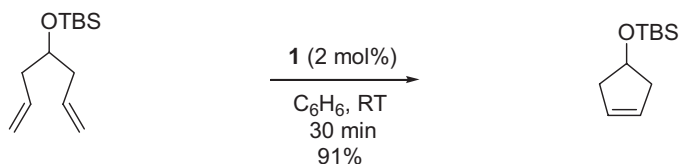
2.2.2

Synthesis of Carbocycles

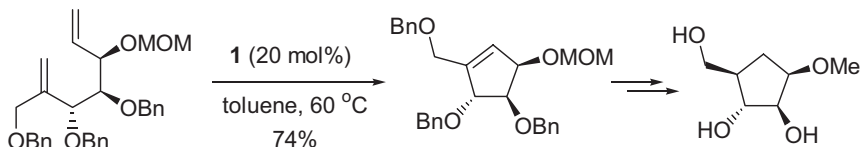
2.2.2.1

Carbocyclization

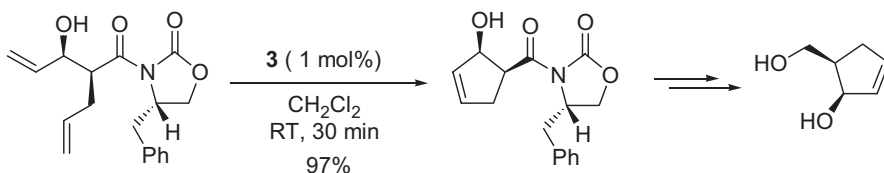
The first example of carbocyclization by a well-defined metal-carbene catalyst was described by Grubbs [24]. It was demonstrated that cycloalkenes having various substituents with various sizes could be readily obtained with high efficiency

Grubbs *JACS* **1993**, *115*, 3800

Scheme 2.2-2

Lowary *OL* **2000**, *2*, 167

Scheme 2.2-3

Crimmins *JOC* **1996**, *61*, 4192
OL **2000**, *2*, 1065

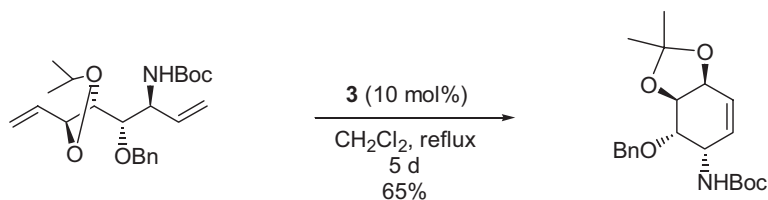
Scheme 2.2-4

(Scheme 2.2-2). It was also shown that groups commonly encountered in synthesis, such as silyl ethers, benzyl ethers, esters, and alcohols, are stable to the reaction conditions.

An efficient total synthesis of arabinofuranosides was recently described by Lowary [25], using RCM as a key step. Metathesis reactions of trisubstituted double bonds were not effective with the ruthenium catalyst **3** to produce the desired cyclopentene in low yield (12–18%). However, cyclization proceeded smoothly in the presence of the molybdenum catalyst **1** to afford the product in moderate yield (Scheme 2.2-3)

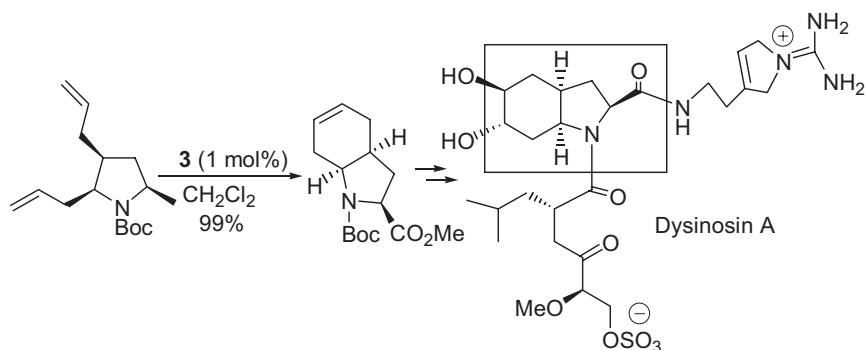
A highly convergent approach has been disclosed by Crimmins [26–28] for the synthesis of carbocyclic nucleosides utilizing RCM as a key step. The ring-closure reaction of the diene bearing a chiral auxiliary proceeded with high efficiency to furnish cyclopentenol (Scheme 2.2-4)

Construction of highly functionalized and stereodefined carbocycles has been reported by Boom [29] based on RCM strategy. RCM of fully functionalized



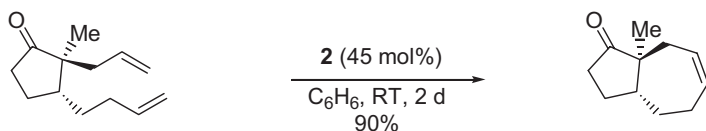
Boom *TL* **1999**, 40, 5063

Scheme 2.2-5



Hanessian *JACS* **2002**, 124, 13342

Scheme 2.2-6



Blechert *Tetrahedron* **1995**, 51, 13003

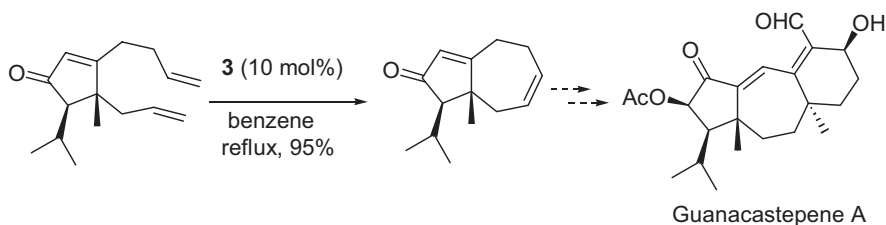
Scheme 2.2-7

1,7-diene proceeds at a slow rate (heating for 5 days) to produce conduramine in moderate yield (Scheme 2.2-5). The corresponding substrate with an *N*-trichloroactetyl protecting group instead of Boc group did not undergo the RCM.

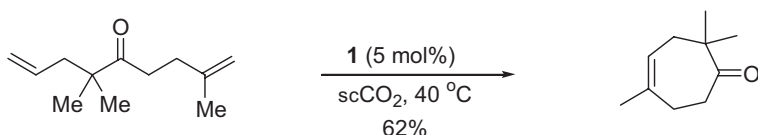
Recently, Hanessian reported the elegant use of RCM in the total synthesis of a marine natural product, dysinosin A (Scheme 2.2-6) [30].

Blechert showed that RCM is very useful for the preparation of a wide range of substituted hydroazulenes [31]. Cyclopentanone precursors underwent efficient cyclization upon treatment with **2** in excellent yields (Scheme 2.2-7).

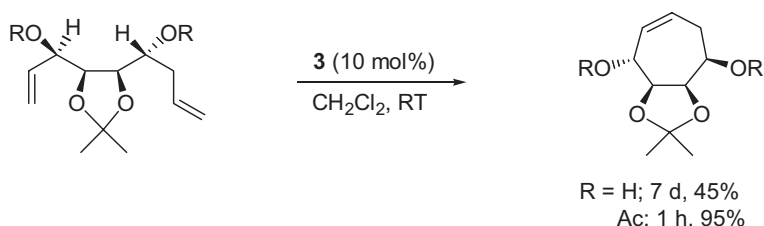
Mehta successfully constructed the hydroazulenic core in the diterpene antibiotic guanacastepene A by employing RCM reaction as the key step, thereby enabling

Mehta *OL* **2002**, 4, 1063

Scheme 2.2-8

Fürstner *ACIEE* **1997**, 36, 2466

Scheme 2.2-9

Marco-Contelles *JOC* **2000**, 65, 5416

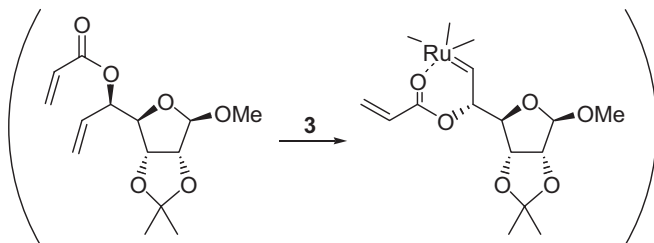
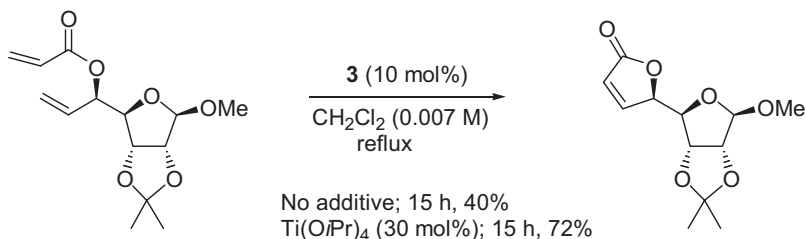
Scheme 2.2-10

generation of the 7-membered ring to access the hydroazulenenic framework (Scheme 2.2-8) [32].

Fürstner investigated successful applications of RCM in supercritical carbon dioxide as a feasible reaction medium [33]. Reaction of a dienone substrate with the molybdenum catalyst **1** in scCO₂ gave karahanaenone, an olfactory compound contained in hops and cypress oil (Scheme 2.2-9).

As another example, Marco-Contelles has recently described synthesis of polyhydroxylated carbocycles starting from carbohydrates [34, 35]. Carbocyclization of a diene bearing a diacetate-protecting group gave the cycloheptene derivative with high efficiency (Scheme 2.2-10). In contrast, RCM reaction of non-protected diol proceeded at a slower rate and in lower yields.

It is generally known that the RCM of diene substrates bearing a γ,δ - or β,γ -unsaturated carbonyl moiety does not proceed at all. This is mainly attributed to



Ghosh *TL* **1998**, 39, 4651

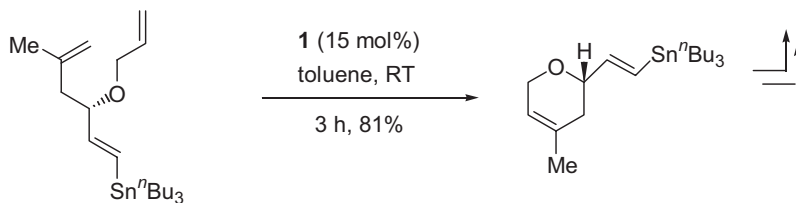
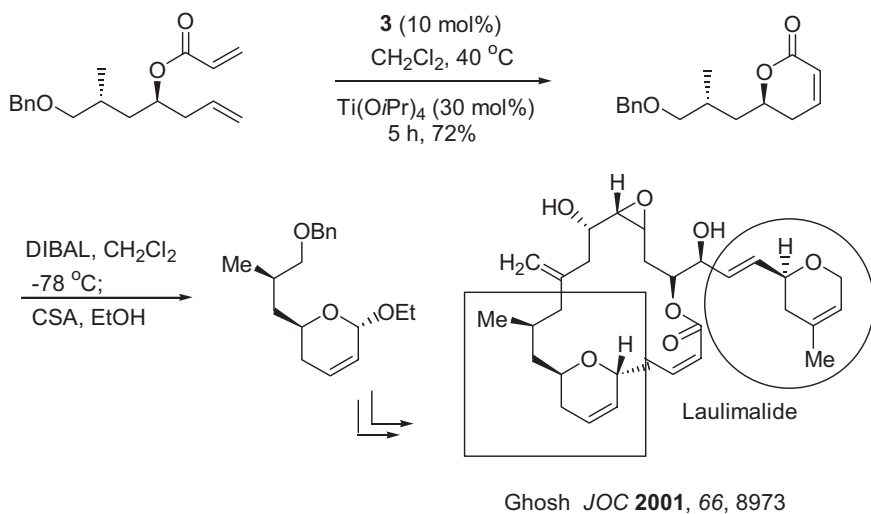
Scheme 2.2-11

the formation of a stable and thus inactive 6- or 7-membered Ru-chelation complex that blocks the catalytic cycle. To prevent the chelation and therefore to proceed with the RCM of carbonyl substrates, certain Lewis acids such as Ti(OiPr)_4 have been added in catalytic amounts to the metathesis reaction mixtures. For example, metathesis reaction of an acrylate ester gave lower conversion (40%), even after prolonged reaction times with the ruthenium catalyst **3** only. In contrast, the reaction was significantly accelerated and gave much higher yields with addition of Ti(OiPr)_4 to the metathesis reaction conditions (Scheme 2.2-11) [36, 37].

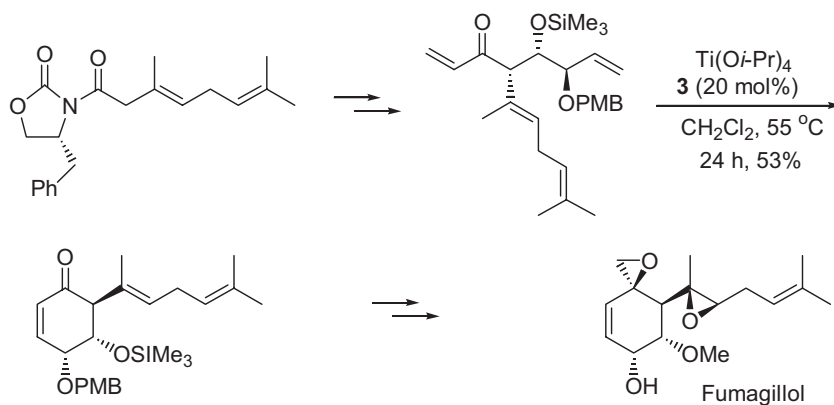
Ghosh later applied the same method in his approach to the total synthesis of (–)-laulimalide (Scheme 2.2-12) [38, 39]. Nelson also completed the total synthesis of the same natural product by utilizing a Mo(VI)-based metathesis catalyst in mediating the desired pyran ring formation. The RCM of the stannyl alkene precursor exhibited a kinetic preference for engaging the mono- and 1,1-disubstituted olefins in 6-membered ring formation rather than the sterically more encumbered 1,2-disubstituted product [40].

During the synthesis of an anti-angiogenic agent, (–)-fumagillol, the key cyclohexenone intermediate was prepared by an Evans aldolization and RCM of the corresponding enone (Scheme 2.2-13) [41]. Several reaction conditions were examined in order to achieve the 6-membered ring closure. Construction of the desired cyclohexenone moiety was accomplished by the RCM reaction using catalyst **3** in the presence of Ti(Oi-Pr)_4 in dichloromethane as the solvent.

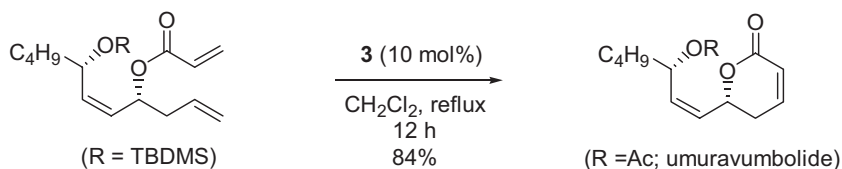
Even though electron-deficient dienic systems (containing α,β -unsaturated esters



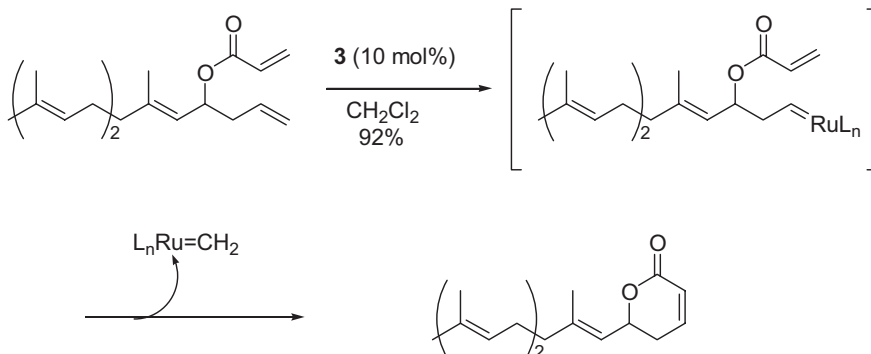
Scheme 2.2-12



Scheme 2.2-13

Ramachandran *OL* **2001**, 3, 19

Scheme 2.2-14

Wiemer *TL* **2001**, 42, 6069

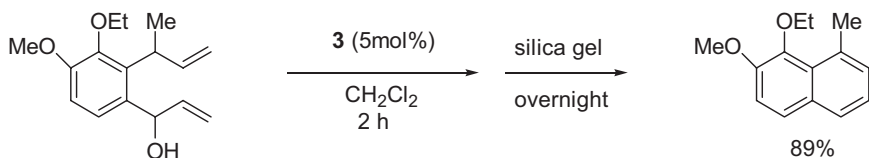
Scheme 2.2-15

and amides) are known to be relatively poorly reactive in RCM reaction and generally require Lewis acid catalysis, the presence of certain Lewis acids is not always mandatory for the efficient RCM of α - or β -carbonyl olefin substrates, depending on the conformational structures of the dienes. For example, RCM of an α -carbonyl diene, shown in Scheme 2.2-14, underwent the cyclization with excellent efficiency even in the absence of any additional Lewis acids [42, 43].

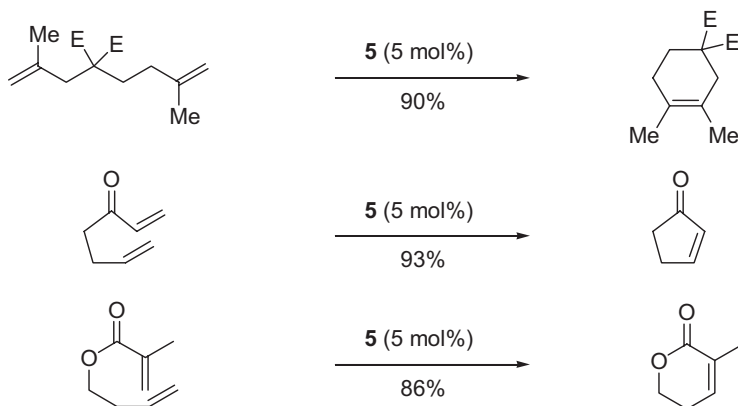
Wiemer reported a regioselective RCM reaction of terpeneoid acrylates and acrylamides derived from allylic and homoallylic alcohols in the presence of the other double bonds. As shown in Scheme 2.2-15, less substituted olefins in a close distance preferably underwent RCM, whereas the tri- and geminally disubstituted double bonds did not participate in RCM with catalyst **3** [44].

A practical method for the preparation of multi-substituted naphthalenes was disclosed via RCM (Scheme 2.2-16) [45]. When substrates were treated with catalyst **3**, ring closure occurred, followed by dehydration *in situ* in the presence of silica gel, to afford the naphthalene derivatives.

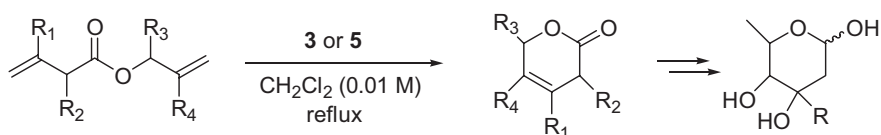
The new type of ruthenium catalysts **4** and **5** bearing *N*-heterocyclic carbene ligands displayed unique activity toward previously metathesis-inactive (or low active) substrates due to their higher activity and improved stability. In fact, complex **5** can catalyze with high efficiency the RCM reactions in cases where the

Wang *TL* **2001**, 42, 6155

Scheme 2.2-16

Grubbs *OL* **1999**, 1, 953
JACS **2000**, 122, 3783

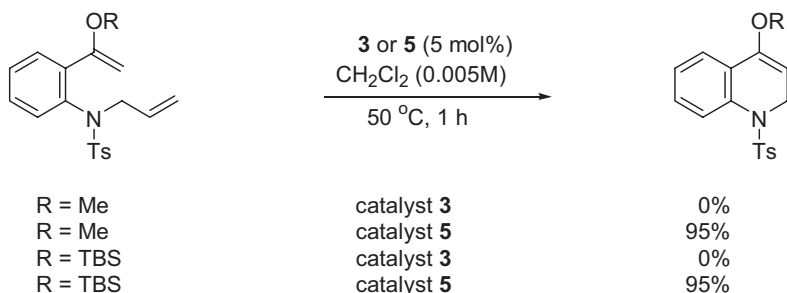
Scheme 2.2-17

 $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4 = \text{H or CH}_3$ Wang *OL* **2002**, 4, 3875

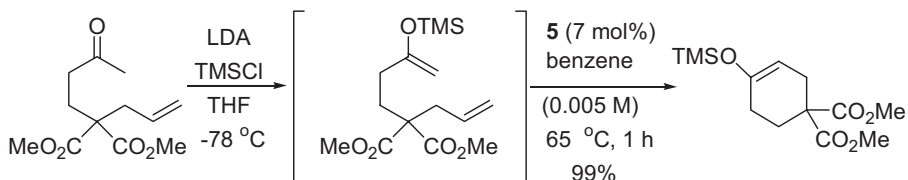
Scheme 2.2-18

Mo complex **1** or the most widely used ruthenium complex **3** does not. For substrates such as α -carbonyl, alkenes are now cleanly cyclized into various sizes of α, β -unsaturated carbonyl compounds in respectable yields, even in the absence of any additional Lewis acids (Scheme 2.2-17) [10, 46].

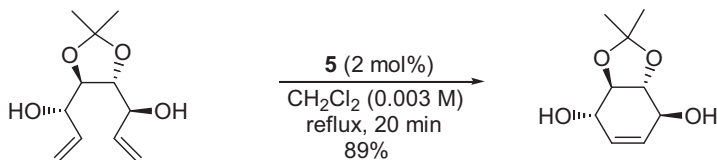
Wang utilized RCM in the construction of β, γ -unsaturated δ -lactones. Catalyst **5** worked best on a 1 mol% scale and afforded higher yield, whereas catalyst **3** worked best at 5 mol% and lower yield (Scheme 2.2-18). Asymmetric dihydroxylation and reduction led to biologically important 2,6-dideoxysugars [47].

Nakagawa *TL* **2001**, 42, 8029

Scheme 2.2-19

Shibasaki *TL* **2001**, 42, 8023

Scheme 2.2-20

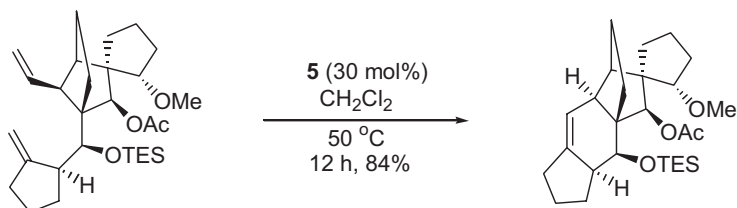
Bertozzi *OL* **2002**, 4, 1359

Scheme 2.2-21

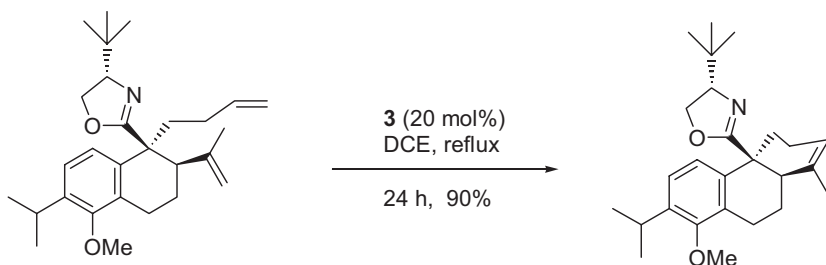
Nakagawa reported a convenient method for quinoline synthesis using RCM with ene-enol ether. When catalyst **5** was used, the RCM reaction proceeded excellently, whereas catalyst **3** gave no cyclized product (Scheme 2.2-19) [48].

Shibasaki also synthesized cyclic enol ethers from corresponding acyclic alkenyl ketones or acyclic alkenyl silyl ethers in excellent yield using RCM in two steps (Scheme 2.2-20) [49].

Stereoselective synthesis of *myo*-inositol analogue as a building block for glycosylphosphatidylinositol anchor was achieved via RCM [50]. The increased reactivity of catalyst **5** permitted the use of an acetal functionality on preexisting hydroxyl groups and thus allowed the facile differentiation of the hydroxyl groups for efficient synthesis of the *myo*-inositol (Scheme 2.2-21).

Nicolaou CC **2002**, 2480

Scheme 2.2-22

Meyers *Synthesis* **2002**, 2064

Scheme 2.2-23

The synthesis of the fused polycyclic carbon framework of vannusal A was completed by RCM reaction using catalyst **5** (Scheme 2.2-22) [51]. Thus, the cyclohexene ring was elegantly installed in the fused polycyclic system. This work represents the power of modern synthetic technologies, such as RCM, to construct complex molecular architectures.

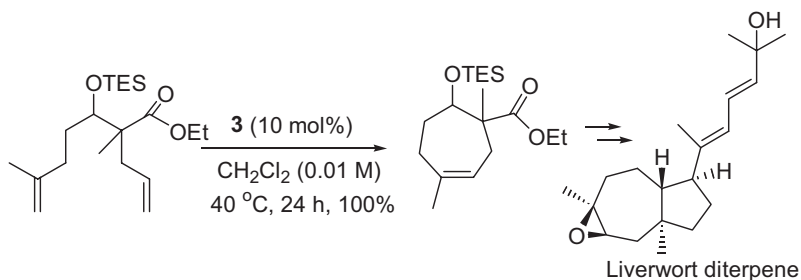
Meyers reported a successful RCM reaction in the presence of a chiral basic oxazoline for the first time [52]. Thus, the tricyclic ring core of a natural diterpenoid, (+)-triptinin A, was safely installed via RCM in 90% yield (Scheme 2.2-23).

Seven-membered cyclic compounds possessing trisubstituted double bonds were smoothly synthesized when employing ruthenium complex **3** in the RCM reaction. The product was further converted to the liverwort diterpene (Scheme 2.2-24) [53].

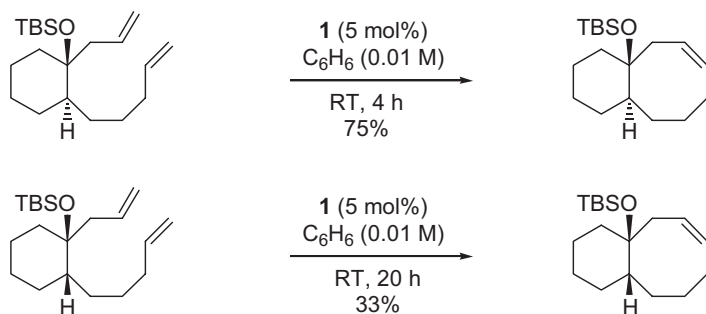
2.2.2.2

Medium-Sized Carbocycles

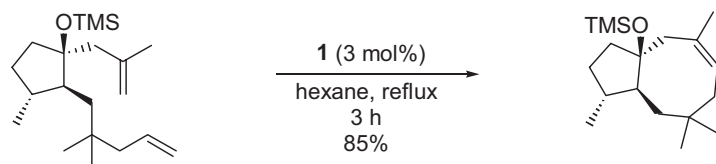
Although RCM has been enormously used for the formation of variable sizes of carbo- and heterocycles, the formation of 8-membered rings via metathesis has been documented much less frequently due to the entropic and enthalpic factors. The initial scope of RCM for 8-membered ring synthesis was disclosed by Grubbs' group, and it was found that the presence of conformational constraints in substrates made the ring closure more facile. While the *trans*-substituted cyclohexanes

Tori *JOC* **2002**, 67, 6034

Scheme 2.2-24

Grubbs *JACS* **1995**, 117, 2108

Scheme 2.2-25

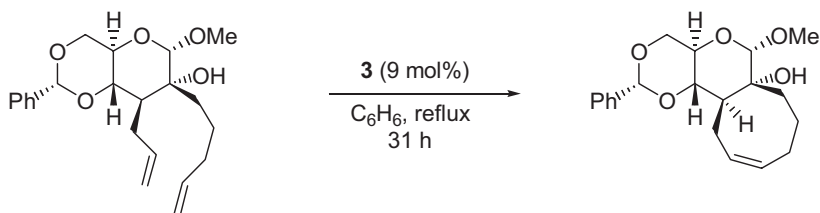
Füster *JOC* **1996**, 61, 8746

Scheme 2.2-26

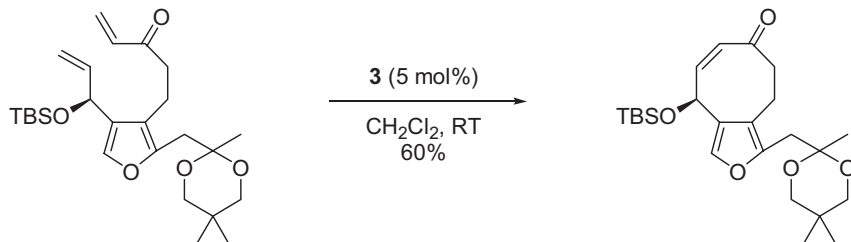
turned out to be good substrates for RCM to afford the bicyclic [6,4,0] systems, the *cis*-isomers reacted slowly to yield the products in lower amounts (Scheme 2.2-25) [54].

A short synthesis of cyclooctenoid sesquiterpene, (\pm)-dactyol, using RCM as a key step [55]. RCM of *O*-silylated diene with the molybdenum catalyst **1** followed by desilylation gave dactyol in respectable yield (Scheme 2.2-26).

Jenkins explored the use of RCM in carbohydrate annulation reactions [56]. Fused bicyclic *cis*-diene was reacted with **3** to furnish tricyclic cyclooctene de-

Jenkins *ACIEE* **1998**, 37, 3298

Scheme 2.2-27

Paquette *OL* **2000**, 2, 1259

Scheme 2.2-28

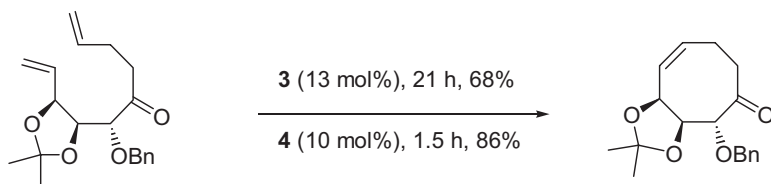
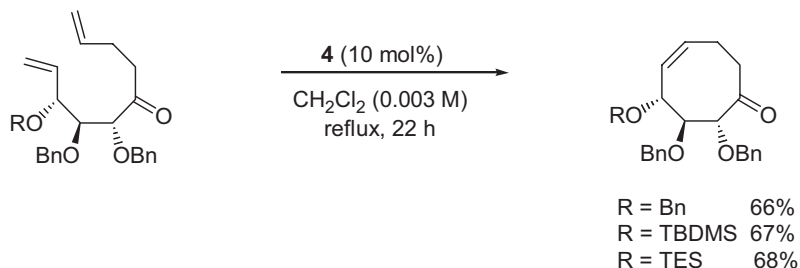
rivatives in moderate yield (Scheme 2.2-27). *Trans* analogues were converted into the *trans* tricyclic ethers in lower yields.

The 8-membered enone was isolated in good yield after removing all colored ruthenium and phosphine impurities of RCM reaction by treating with lead tetraacetate (1.5 equivalent relative to the amount of catalyst) (Scheme 2.2-28) [57].

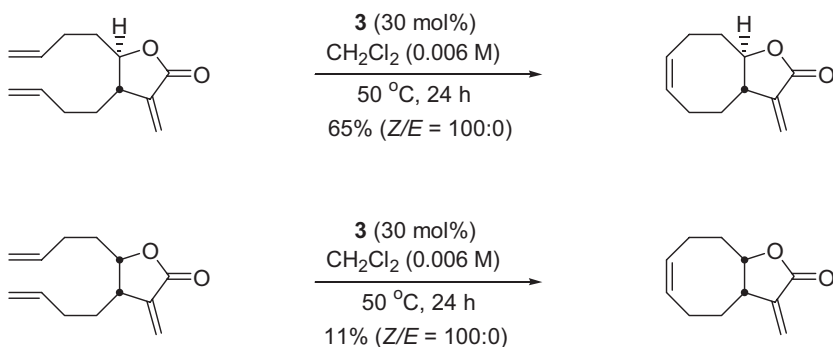
Use of carbohydrates as chiral templates for the formation of carbocycles is of great interest in the synthesis of optically active natural products. Hanna reported successful transformation of carbohydrates to polyoxygenated cyclooctenes via RCM [58]. Ruthenium catalyst **4** was more effective compared with **3**, and RCM proceeded more smoothly in the presence of an acetonide group, due to pre-organized conformational constraint (Scheme 2.2-29).

Paquette recently described a ring-closing metathesis of *trans*-lactone with the ruthenium catalyst **3** to give fused 8-membered α -methylene- γ -lactone, which is a common structural subunit in biologically active natural products (Scheme 2.2-30) [59]. The *cis*-lactone gave the cyclized products in much lower yields, due to ring strain and an elevated barrier to ring closure.

During the studies toward synthesis of taxol and taxotere, Prunet described a cyclization method for highly functionalized precursors of the BC ring system of taxol based on RCM [60]. RCM of a diene was effected with the molybdenum catalyst **1**, leading to cyclooctene in excellent yield, although 3 days were necessary for completion (Scheme 2.2-31). When the diol was protected as a cyclic carbonate, only one diastereomer cyclized to afford a *trans*-cyclooctene for the first time by RCM.

Hanna *JOC* **2001**, 66, 4094

Scheme 2.2-29

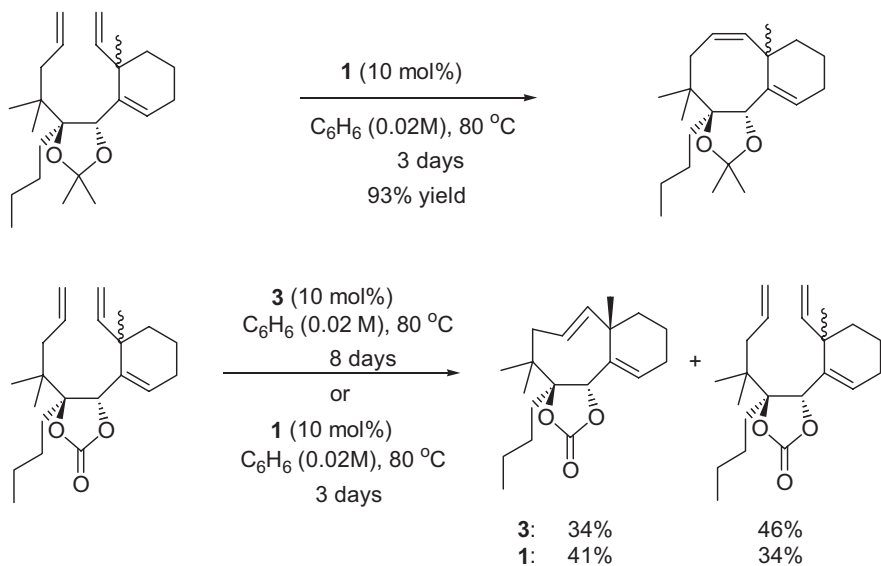
Paquette *ASC* **2002**, 344, 303

Scheme 2.2-30

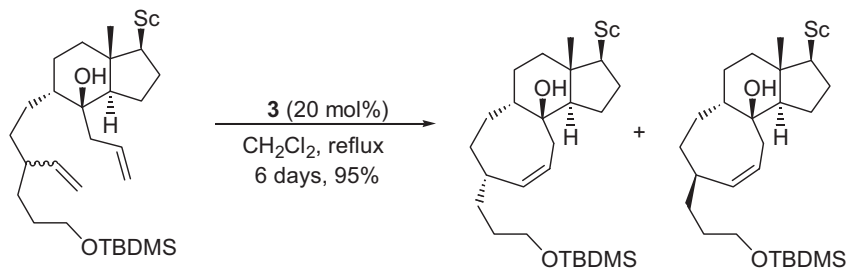
Another example of the synthesis of 8-membered carbocycle using RCM was recently reported by Granja in the synthesis of linearly fused 6-8-6 carbocyclic systems (Scheme 2.2-32) [61]. RCM of the diene substrates with catalyst **3** furnished the cyclooctene derivatives in excellent yield.

Krafft described synthesis of an “inside-outside” tricyclic ring system by RCM [62]. Cyclization of bicyclic diene with the ruthenium catalyst **3** furnished an 8-membered ring bearing an in-out-intra-bridgehead stereochemical relationship, which is a precursor of asteriscanolide (Scheme 2.2-33).

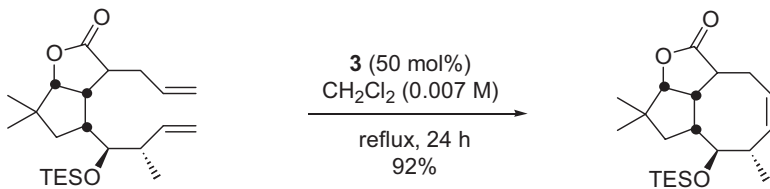
Buszek reported the total synthesis of a lactone natural product, octalactin A, via RCM reaction as the key step (Scheme 2.2-34) [63]. The position of certain stereo-

Prunet *ACIEE* **2000**, 39, 726

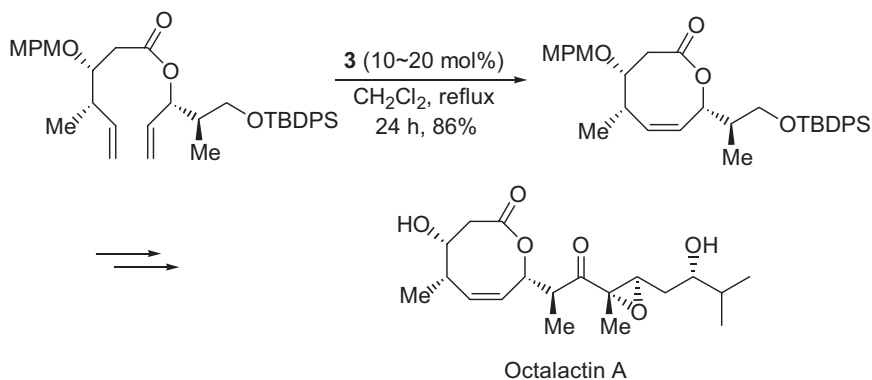
Scheme 2.2-31

Granja *OL* **2002**, 4, 1651

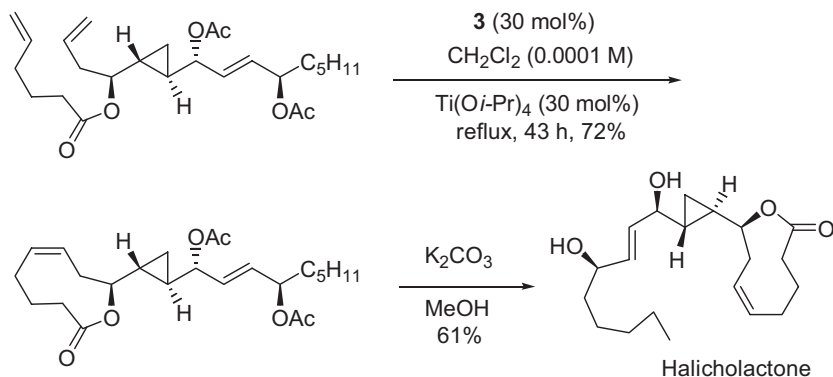
Scheme 2.2-32

Krafft *Synthesis* **2000**, 1020

Scheme 2.2-33

Buszek *TL* **2002**, 43, 181

Scheme 2.2-34

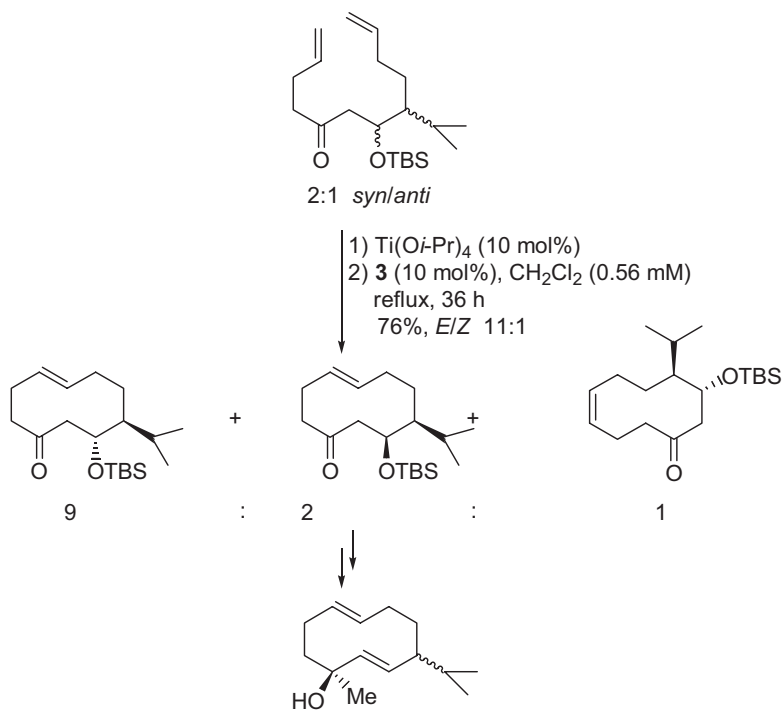
Takemoto *JOC* **2001**, 66, 81

Scheme 2.2-35

centers on the substrate was critical in the RCM, indicating that the conformational constraints imposed by the stereocenters favored the reactive diene conformation to afford the 8-membered lactone core in good yield. This is the first example of the synthesis of monocyclic 8-membered ring lactones by RCM.

During the total synthesis of a natural lipoxygenase inhibitor, halicholactone, Takemoto utilized RCM as the key step for the formation of a 9-membered unsaturated lactone fragment (Scheme 2.2-35) [64]. The RCM reaction proceeded smoothly with catalyst **3** in the presence of $\text{Ti}(\text{O}i\text{-Pr})_4$ under highly diluted conditions (0.1 mM) to afford the desired *Z*-isomer (72%) along with the dimer (11%). The (*Z*)-selectivity in RCM was exclusively observed under the reaction condition.

The 10-membered carbocycle via RCM was first reported in 2001. During the course of the synthesis of a sesquiterpene analogue, nor-1,6-germacradien-5-ol,



Koskinen *ACIEE* **2001**, 40, 4060
JOC **2002**, 67, 1554

Scheme 2.2-36

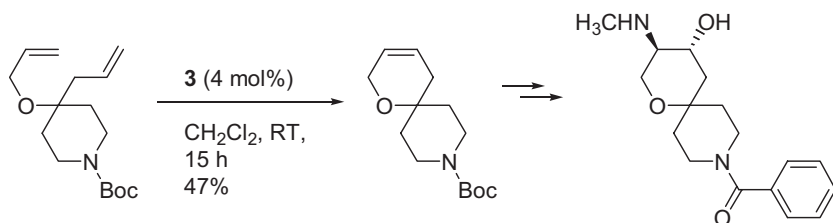
derived from the resin of pine trees, Koskinen elaborated the RCM methodology with a bis-olefin for the formation of a 10-membered ring (Scheme 2.2-36) [65, 66]. Coordination of the Lewis acid to the carbonyl group during RCM may be responsible in part for conformational restriction on the bis-olefin to increase the catalytic activity to ward the desired target.

2.2.2.3

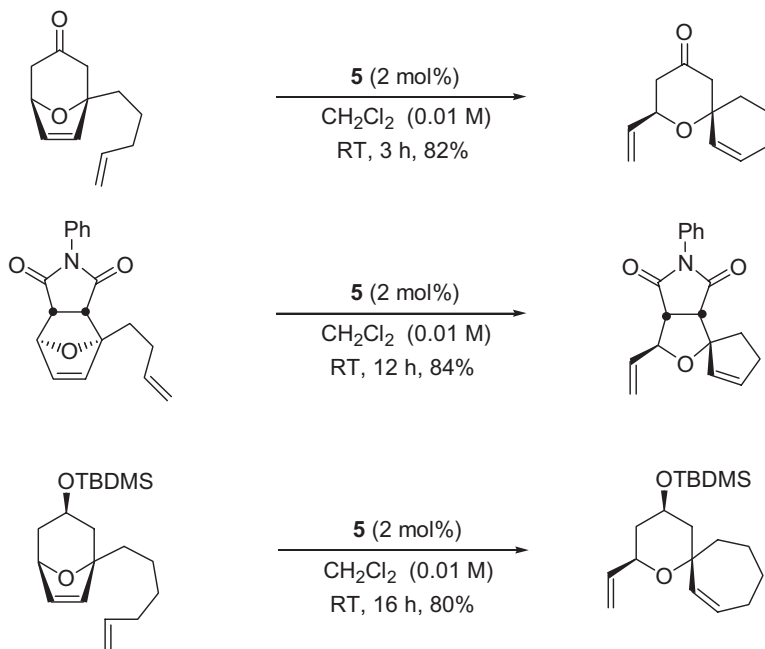
Spiro Carbocycles

Walters reported the preparation of a readily functionalized, spirocyclic template via RCM and its use in the preparation of libraries of novel compounds, such as a spirocyclic amino alcohol library, using combinatorial techniques (Scheme 2.2-37) [67].

Wright successfully synthesized spirocyclic pyrans and perhydrofurans from a series of oxabicyclo compounds with an olefinic tether at the bridgehead using domino ring-opening/ring-closing metathesis reactions (Scheme 2.2-38) [68]. Manipulations of functional groups on the substrates played an important part in the reactivity and selectivity of the metathesis reactions.

Walters *JCC* **2002**, 4, 125

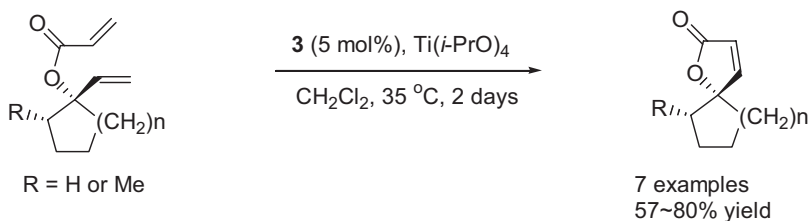
Scheme 2.2-37

Wright *ACIEE* **2002**, 41, 4560

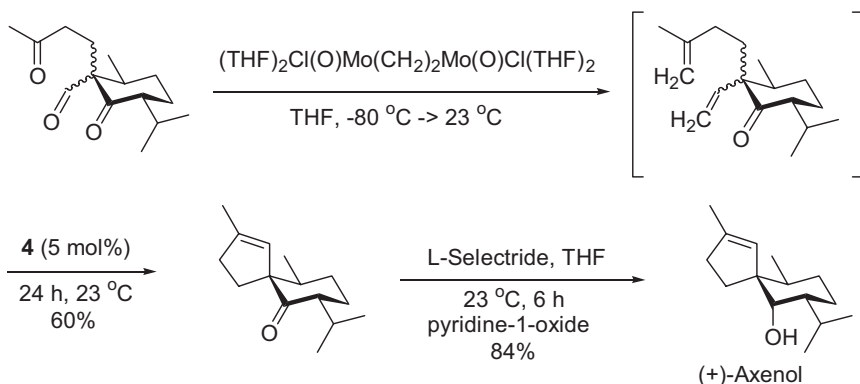
Scheme 2.2-38

Spirocyclic butenolides were efficiently synthesized by Langer using an RCM reaction (Scheme 2.2-39) [69].

Spitzner synthesized a marine sesquiterpene alcohol, (+)-axenol, in few steps from (+)-menthone using a “one-pot” olefination-RCM reaction (Scheme 2.2-40) [70]. One-pot synthesis protocol generally increases the synthetic efficiency. However, olefination of a carbonyl by Wittig reaction followed by metathesis in an one-pot reaction cannot be easily combined due to the sensitivity of the commercially available RCM catalyst toward phosphines or phosphine oxides generated during

Langer *Synlett* **2002**, 1841

Scheme 2.2-39

Spitzner *Synlett* **2002**, 1712

Scheme 2.2-40

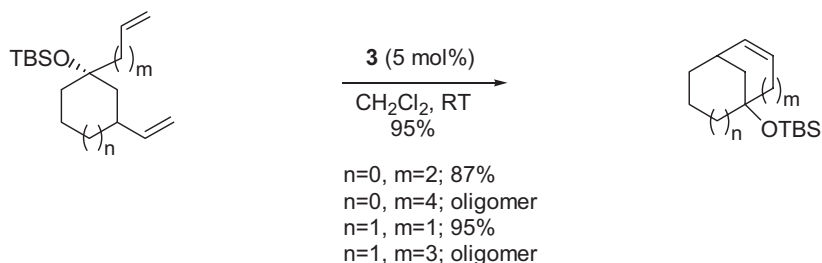
the reaction. Only the Tebbe olefination might be useful for this type of reaction. The successful olefination with Mo complex and RCM with the ruthenium catalyst 4 proceeded smoothly to afford the spiroalkene.

2.2.3

Synthesis of Bridged Bicycloalkenes

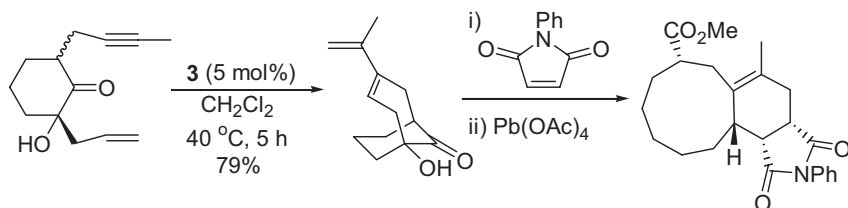
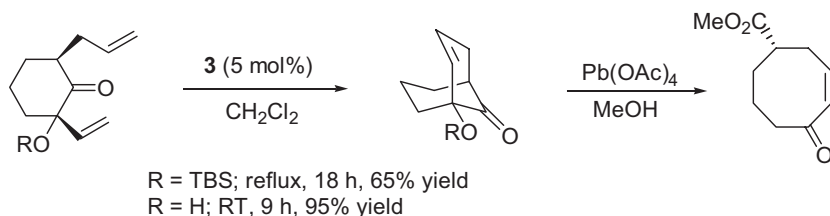
Small-ring bridged bicycloalkenes [*n*,*x*,1] were synthesized using RCM from monocyclic dienes. As expected, the ring closure of 5-, 6-, and 7-membered rings was relatively facile, while reactions for the formation of 8-membered rings did not occur (Scheme 2.2-41) [71]. MM2 calculations indicated that if the calculated enthalpy is less than ca. 10 kcal mol⁻¹, the ring closure should be favorable due to the entropy gain from the generation of ethylene.

The presence of a temporary one-atom internal tether in 1,9-deca- and 1,10-undecadiene allowed their efficient RCM (Scheme 2.2-42) [72]. Interestingly, whereas the RCM of silyl ether diene required more vigorous reaction conditions



Grubbs CC 1998, 275

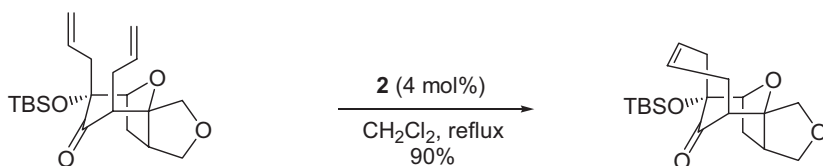
Scheme 2.2-41



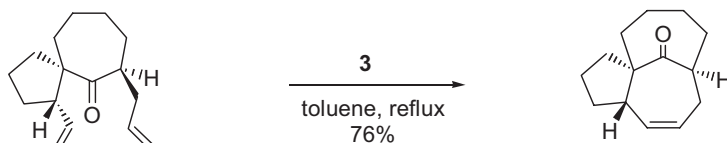
Mascarenas OL 2000, 2, 3209
 CEJ 2002, 8, 2923

Scheme 2.2-42

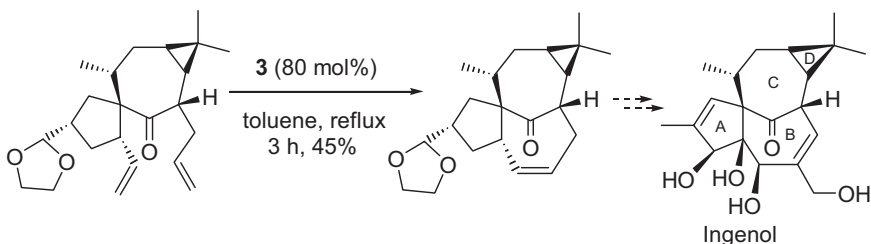
and gave lower yield, free alcohol substrate smoothly cyclized at room temperature with much higher yield. This notable rate difference was attributed to the relative equilibrium between two possible conformations in each case. When $\text{R} = \text{H}$, *cis*-conformation was more easily reached due to the existence of an intramolecular H bond between the hydroxyl and carbonyl groups. Cleavage of the bridged tether of the resulting bicycles provides 8- and 9-membered carbocycles. Mascarenas also disclosed the synthesis of ring-fused carbocycles through an RCM/ring fragmentation strategy [73]. Especially when enyne substrates were used in the RCM condition, a bridged bicyclo-1,3-diene system was installed. These bridged bicycles underwent stereoselective Diels-Alder reaction to afford 8-6 or 9-6 fused bicarbocycles after oxidative cleavage of the keto bridge of the resulting tricycles.

Mascarenas *JOC* **1997**, 62, 8620

Scheme 2.2-43

Uemura *TL* **2000**, 41, 3927

Scheme 2.2-44

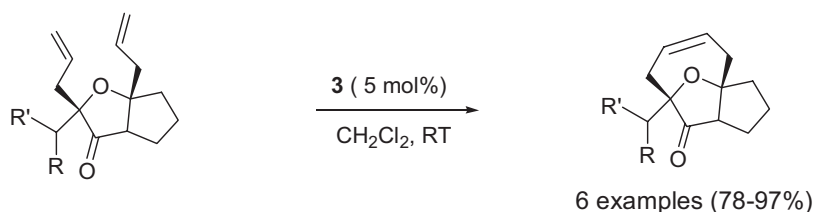
Wood *OL* **2001**, 3, 1563

Scheme 2.2-45

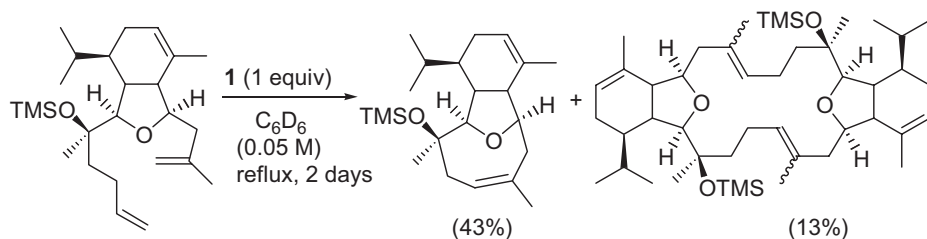
Highly complex tricyclic dienes underwent ring-closing metathesis with **2** to give tetracyclic olefins in excellent yields (Scheme 2.2-43) [74]. Subsequent reduction, silyl deprotection, and oxidative ring expansions provided stereochemically rich *cis*-2,5-disubstituted tetrahydrofurans, leading to 9- and 10-membered carbocycles whose ring types are present in numerous naturally occurring terpenoids.

Uemura prepared *in,out*-tricyclo[7.4.1.0^{1,5}]tetradecan-14-one by direct cyclization using olefin metathesis (Scheme 2.2-44) [75]. Whereas the allyl ketone substrate was cyclized to give the tricycloketone system in good yield even under rather vigorous reaction conditions, reaction of its allylic epimer was more sluggish and resulted in a lower yield (20%) of the cyclized product.

Similarly, in an effort to synthesize a natural product, ingenol, Wood reported the synthesis of the complete carbocyclic skeleton via a route that employs the robust RCM to close the strained “inside-outside” BC ring system (Scheme 2.2-45) [76]. Since the A and B rings of the RCM product have the appropriate functionality, they should permit elaboration to the natural product.

Hanna *OL* **2000**, 2, 1141

Scheme 2.2-46

Overman *TL* **1997**, 38, 8635

Scheme 2.2-47

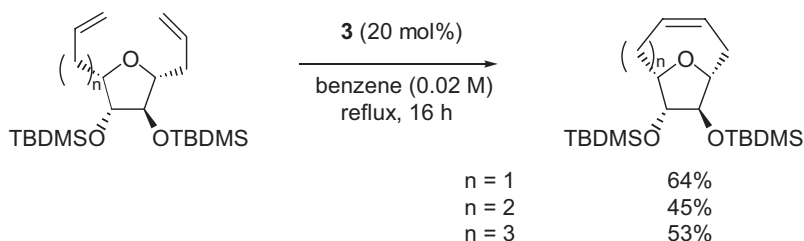
Carbocyclization of 2,3-disubstituted-1,4-dioxenes by **3** (5 mol%) was efficiently carried out under mild conditions to afford 9-oxabicyclo[4,2,1]nonene compounds in excellent yields (Scheme 2.2-46) [77]. Cleavage of the *oxa*-bridge of the products can lead to the 5,8-fused ring system present in many natural compounds.

Overman observed an interesting result in an attempt to synthesize eunicellin diterpenes by RCM [78]. While cyclization of the siloxytriene with **3** was unsuccessful, the same reaction with 1 equivalent of the molybdenum complex **1** gave a siloxytricycle as a major product, in which the newly formed ring was surprisingly one carbon unit smaller than expected (Scheme 2.2-47). Metal-induced isomerization of the monosubstituted terminal olefin into internal position followed by cyclization via metathesis was attributed as a possible explanation for this result.

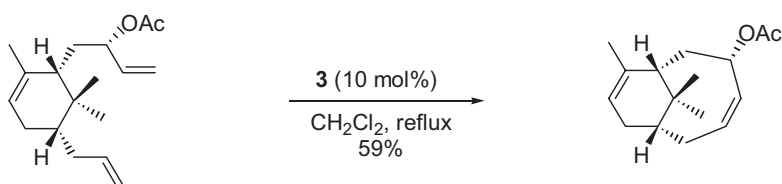
Another example of the synthesis of medium-sized ring-bridged oxabicycles by RCM was recently reported (Scheme 2.2-48) [79]. Both optical antipodes of the oxabicyclo[4.2.1]-, -[5.2.1]-, and -[6.2.1]alkenes were enantioselectively constructed via RCM reaction of the suitable 2,5-*cis*-dialkenyltetrahydrofuran derivatives.

Bleichert described the first known RCM approach to enantiomerically pure taxol A/B ring fragments [80]. Application of **3** to triene afforded bicyclic acetate in moderate yield (Scheme 2.2-49).

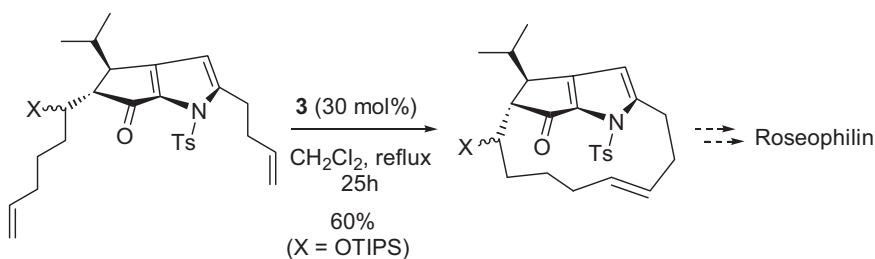
The tricyclic core of roseophilin was prepared using RCM as a key step [81, 82]. Cyclization was shown to proceed, as seen in many examples of conformationally unrestricted acyclic olefins, only with appropriate structural restraints. While metathesis of non-substituted substrate ($\text{X} = \text{H}$) with **3** at low concentrations

Armas *EJOC* **2001**, 3, 4423

Scheme 2.2-48

Blechert *Synthesis* **1999**, 607

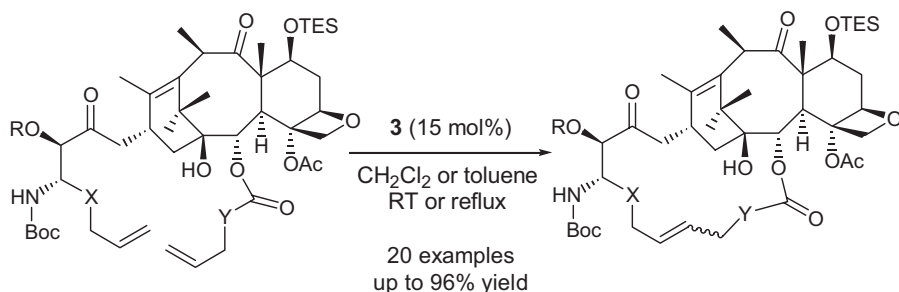
Scheme 2.2-49

Fuchs *TL* **1996**, 37, 2545
TL **1997**, 38, 2601

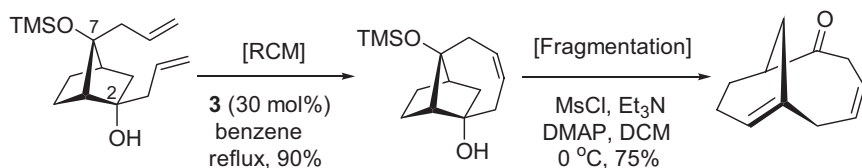
Scheme 2.2-50

afforded only macrocyclic dimers, cyclization of a substrate having a side chain (X = OTIPS) provided the desired *ansa*-bridged silyl ether product in moderate yield (Scheme 2.2-50).

Ojima reported a series of novel macrocyclic taxoids bearing 16-, 17-, and 18-membered rings connecting the substituents at the C-2 and C-3' positions using RCM of taxoid- ω, ω' dienes as the key step [83]. The design was made to provide hybrid constructs of taxoids and epothilones. The RCM reactions by **3** (20 mol%) were effected in most cases with remarkably high efficiency considering that the substrates contain many functional groups and possess highly complex structures (Scheme 2.2-51). It is notable that the stereochemistry of the double bond formed

Ojima *JACS* **2000**, 122, 5343

Scheme 2.2-51

Mehta *CC* **2002**, 1456

Scheme 2.2-52

by the RCM of taxoids was predominantly or exclusively *E* in most cases. All synthetic macrocyclic taxoids were found to be cytotoxic. This methodology of RCM in the crucial macrocyclization step was later adopted by Kingston in the synthesis of paclitaxel analogues [84].

Mehta recently reported a norbornyl-based approach to *anti*-Bredt alkenes via sequential RCM and Wharton fragmentation strategy (Scheme 2.2-52) [85]. The key structural element in the norbornyl precursor was the ensemble of the two alkene arms at C2 and C7 projecting on the *exo*- and *syn*- face, respectively, to facilitate the RCM reaction. Catalyst **3** smoothly furnished the tricyclic olefin bearing the bexane framework by RCM. When the hydroxyl group was mesylated, an efficient fragmentation took place to deliver the bridgehead alkene as the *anti*-Bredt product.

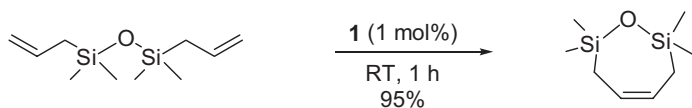
2.2.4

Synthesis of Heterocycles Containing Si, P, S, or B

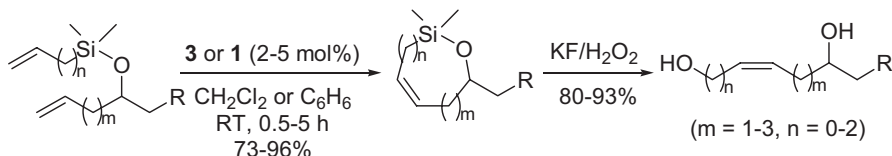
2.2.4.1

Si-Heterocycles

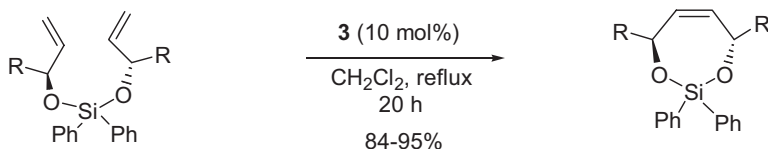
Forbes showed one of the first applications of RCM of silicon heteroatoms. Bis(allyldimethyl)silyl ethers were reacted with **1** under solvent-free conditions to afford cyclic bis-silyl ethers in excellent yields (Scheme 2.2-53) [86].

Forbes *JACS* **1992**, *114*, 10978

Scheme 2.2-53

Grubbs *TL* **1997**, *38*, 4757

Scheme 2.2-54

Evans *JOC* **1998**, *63*, 6768

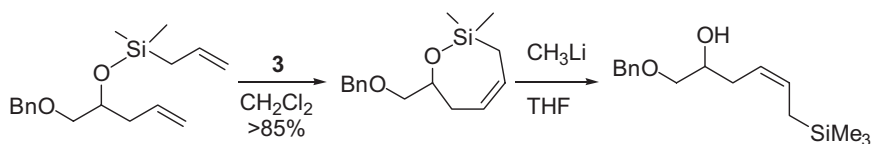
Scheme 2.2-55

RCM of temporary connected dienes and subsequent removal of the tether can afford acyclic alkenes with fixed stereochemistry of the double bonds and with various functionalities. One example was reported from Grubbs' group in which silicon was used as the connecting atom (Scheme 2.2-54) [87]. While RCM of allylic- or homoallylsilyloxy dienes proceeded quantitatively with the ruthenium catalyst **3**, the Mo complex **1** was more effective for sterically demanding vinylsilyl substrates. The newer generation of Ru catalysts will react with vinylsilyloxy dienes. It is notable that formation of 8-membered rings was highly effective for these silicon-tethered alkenes. Subsequent oxidative removal of silicon of the cyclic products afforded the corresponding *cis*-olefinic diols in excellent yields.

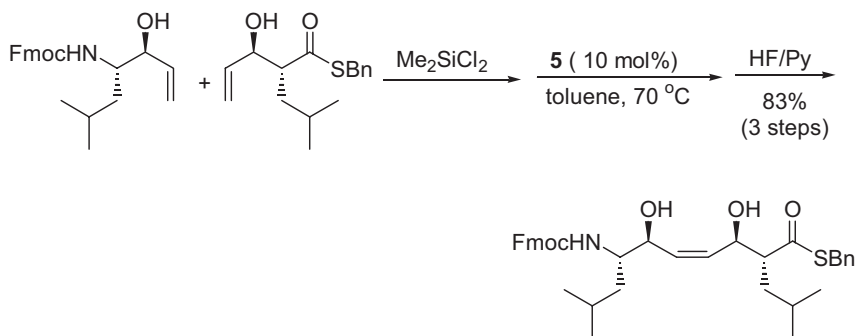
Evans applied similar strategy to obtain diphenyl silaketals as temporary silicon-tethered C_2 -symmetric 1,4-diols (Scheme 2.2-55) [88]. Although reaction times were somewhat long, the cyclic products were obtained in excellent yields in all cases.

Taylor demonstrated in a sequence of reactions that conversion of readily accessible homoallylic alcohols to *trans*-vinylcyclopropanes was possible with high efficiency using RCM as a key step (Scheme 2.2-56) [89].

Another example of the utility of RCM for substrates of silicon-tethered alkenes was shown by Verdine in a synthetic approach to stereo-diversified ligand libraries

Taylor OL **1999**, 1, 1257

Scheme 2.2-56

Verdine OL **2000**, 2, 3999

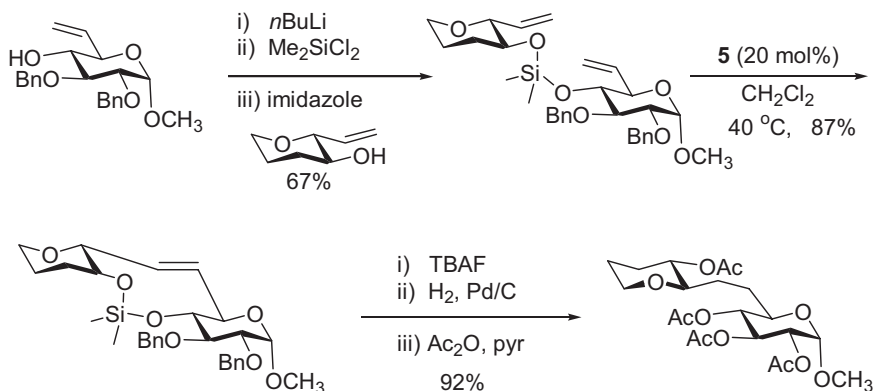
Scheme 2.2-57

[90]. Two units of amino monomers and carboxy monomers were coupled in parallel by silyl-tethered olefin metathesis to generate all stereoisomers of *cis*-enediols after silicon removal (Scheme 2.2-57). In the ring-closure reactions, the newly introduced catalyst **5** exhibited greatly improved activity to give the products in 65–85% yields compared to the more popular catalyst **3**, which performed the reaction in much lower yields (<30%).

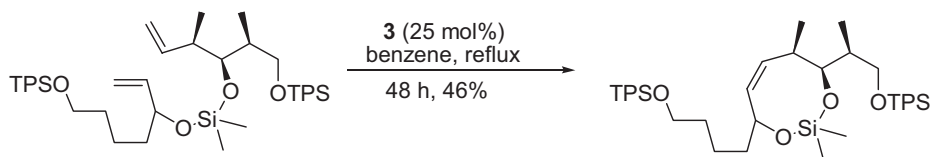
Postema examined RCM reactions of silicon-tethered, carbohydrate-based dienes with catalyst **5** (Scheme 2.2-58) [91]. The two olefinic alcohols were tethered via a Me_2Si linker and subjected to RCM reaction to afford a silicon-containing 9-membered ring as a single *trans* isomer in good yield.

Silicon tether-aided coupling metathesis to afford dissymmetric 8-membered silalketals has appeared for the first time in the literature [92]. Interestingly, the RCM reaction occurred stereoselectively with catalyst **3** (Scheme 2.2-59). On the other hand, catalyst **5** afforded smooth RCM that led to a 1:1 mixture of diastereoisomers, which was converted to the corresponding mixture of diols in 65% yield in two steps. The products were readily converted to spiroketals. This methodology was applied later to the synthesis of a densely functionalized attanol A [93].

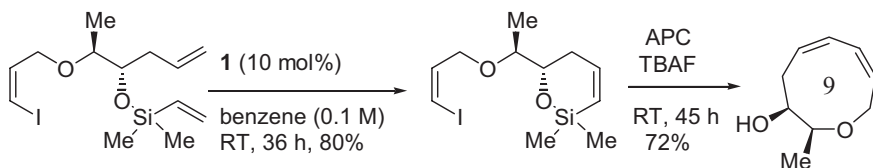
Although a plethora of methods for the synthesis of medium-sized rings exists in the literature, intramolecular silicon-assisted cross-coupling reactions are rare. Denmark reported an elegant method involving the combination of RCM and an

Postema *TL* **2002**, 43, 7095

Scheme 2.2-58

Eustache *TL* **2001**, 42, 239

Scheme 2.2-59

Denmark *JACS* **2002**, 124, 2378

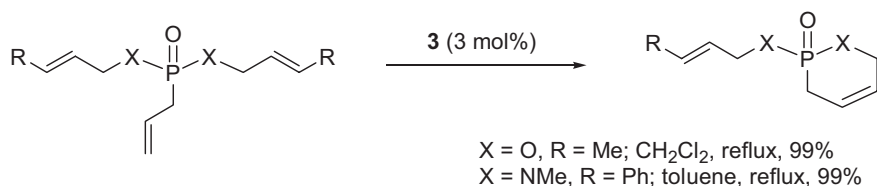
Scheme 2.2-60

intramolecular cross-coupling process to construct medium-sized rings with an internal 1,3-*cis-cis* diene unit (Scheme 2.2-60) [94].

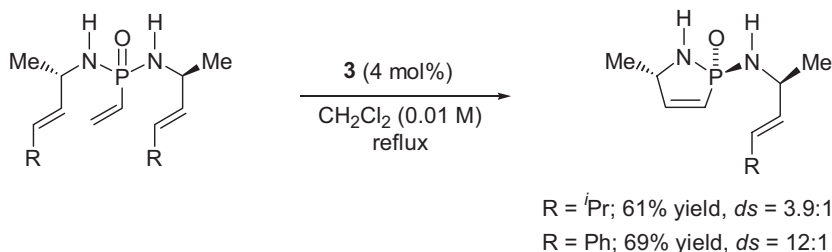
2.2.4.2

P-Heterocycles

Recent reports have shown that alkylidene catalysts could also be applied to RCM of phosphorus-containing substrates. Hanson successfully showed the ring-closing

Hanson *TL* **1998**, 39, 3939*TL* **1999**, 40, 3297

Scheme 2.2-61

Hanson *OL* **2000**, 2, 1769

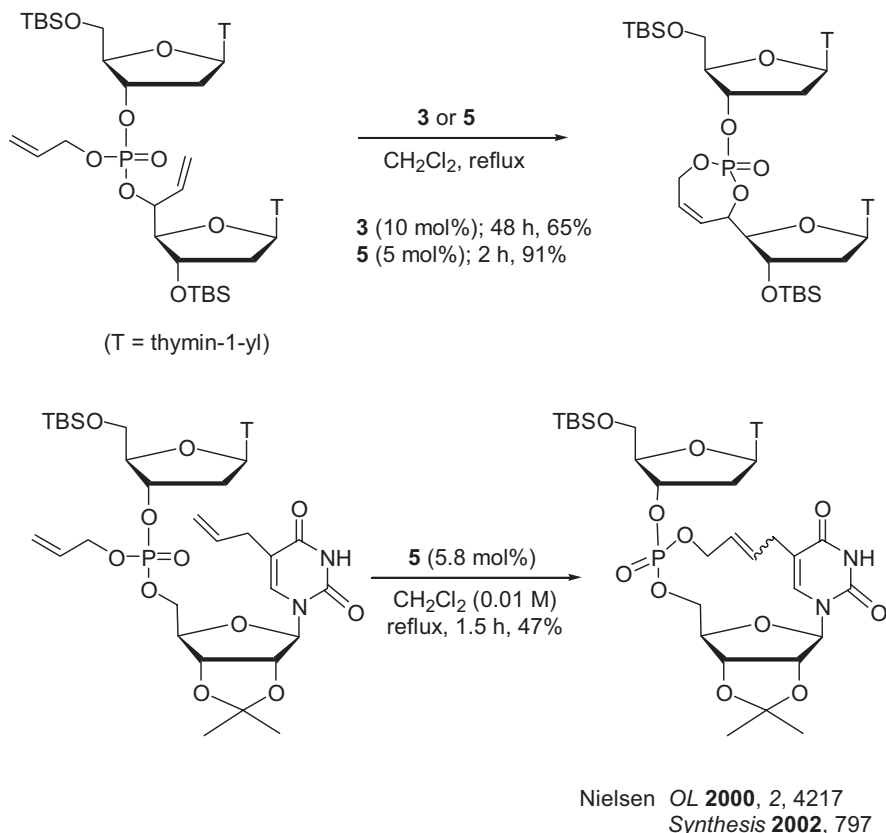
Scheme 2.2-62

metathesis on acyclic phosphonate and phosphonamide templates to give the corresponding cyclic olefinic phosphonates and phosphonamides, respectively (Scheme 2.2-61) [95, 96]. He found that the pattern of the olefin substituents was a major factor in determining the efficiency of the metathesis reactions.

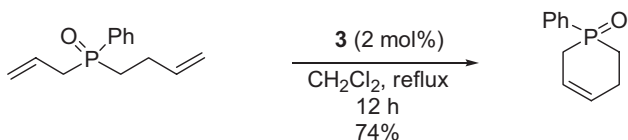
The RCM reaction was employed to desymmetrize a number of pseudo- C_2 -symmetric phosphorus templates [97]. This reaction gave good to excellent levels of selectivity with vinyl phosphonamides containing an (*E*)-Ph group on the diastereotopic olefins (Scheme 2.2-62). This approach was subsequently applied to the synthesis of *P*-chiral amino-acid-derived phosphonamidic anhydrides [98].

Conformational restriction on dinucleotides was successfully introduced by Nielsen using the RCM reaction of the dialkenyl dinucleotides (Scheme 2.2-63) [99, 100]. Compared to **3**, the more recently introduced ruthenium catalyst **5** exhibited much higher reactivity with the nucleotide substrates. This study clearly demonstrated that the RCM reaction was perfectly compatible with the chemistry of nucleotide structures. Similarly, a dinucleotide containing an allylated phosphor-ester and a 5-allyluridine were subjected to the RCM condition to afford a 14-membered cyclophosphate ring with another class of conformationally restricting nucleic acid structure (Scheme 2.2-63) [101].

It turned out that phosphine oxides were also compatible with the ruthenium-carbene complexes and could be added as another entry into RCM chemistry. The



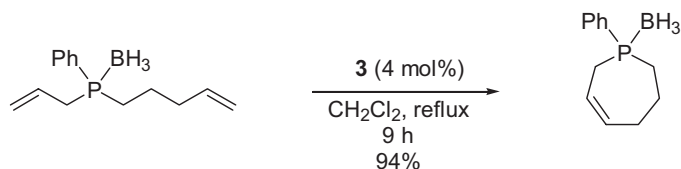
Scheme 2.2-63

Gouverneur *TL* **1999**, 40, 7333

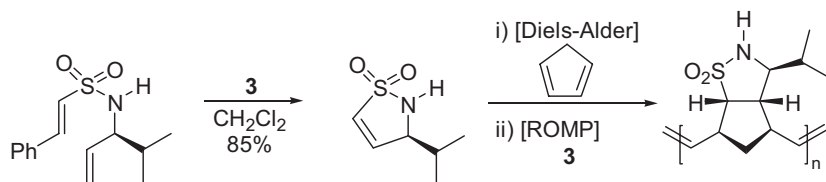
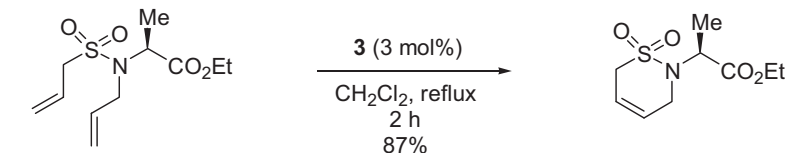
Scheme 2.2-64

ring closure of acyclic diolefinic phosphine oxides was effected in moderate to good yields, depending on the substitution pattern (Scheme 2.2-64) [102].

While the ruthenium catalysts **2** or **3** were ineffective for the ring closure of diallylphenyl phosphanes, presumably due to the ligation of the free phosphorus to the metal center, their borane complexes were found to undergo the RCM reactions smoothly [103]. Formation of 5-, 6-, and 7-membered phosphane rings or bisphosphanes proceeded with high efficiency with **3** (Scheme 2.2-65).

Gouverneur *ACIEE* **2000**, 39, 2491

Scheme 2.2-65

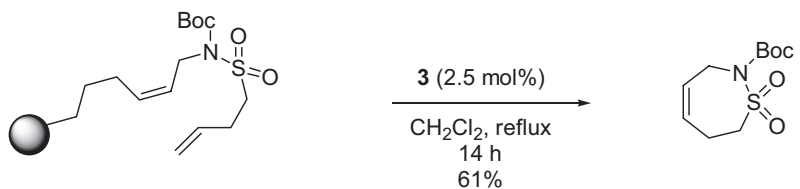
Hanson *TL* **1999**, 40, 4761
TL **2002**, 43, 917

Scheme 2.2-66

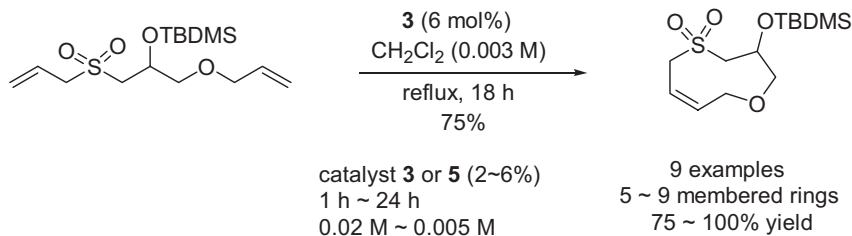
2.2.4.3

S-Heterocycles

Even though tremendous progress in alkene metathesis reactions has been reported, applications of RCM reactions to sulfur-bearing substrates to form sulfur-containing heterocycles are rare. The first example of RCM reaction on allyl- and vinylsulfonamide templates catalyzed by ruthenium carbene was reported by Hanson [104]. The RCM of allylsulfonamides gave good to excellent yields of the allylsultams under the rather mild conditions (Scheme 2.2-66). In contrast, formation of vinylsultams was more sluggish, which is not surprising, because electron-deficient olefins react slowly with substrates in general. Because sulfonamide-containing compounds are ubiquitous in nature as pharmaceutical and agricultural agents, this method for the formation of sulfonamide derivatives should have numerous applications in the future. The α,β -unsaturated γ -sultams, produced by the RCM, were then subjected to the Diels-Alder reaction and ring-opening metathesis polymerization (ROMP) sequentially to afford a variety of sulfonamide oligomers [105].

Brown *TL* **2000**, 41, 3681

Scheme 2.2-67

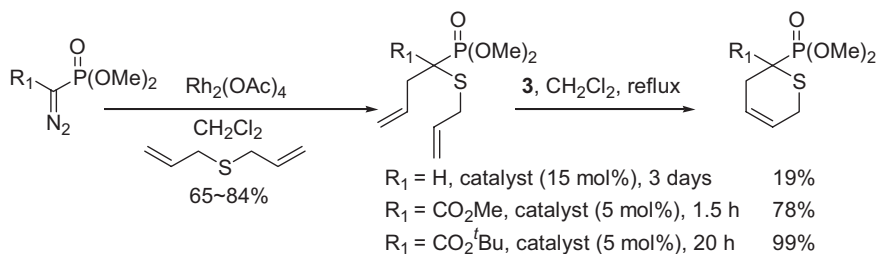
Yao *OL* **2002**, 4, 427

Scheme 2.2-68

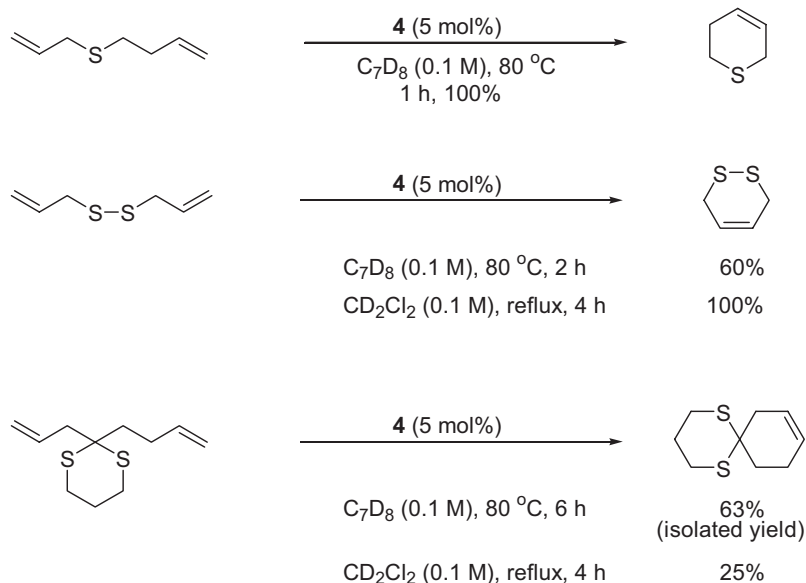
Several novel cyclic sulfonamides were prepared by the application of a solid-phase cyclization-cleavage approach (Scheme 2.2-67) [106]. Flexible linkers were required in order to obtain an efficient release using $\mathbf{3}$ as a metathesis catalyst.

Cyclic sulfones are important subunits and scaffolds for the biologically active molecules and have versatile synthetic utilities. Yao reported a generally applicable and efficient synthesis of cyclic sulfones based on RCM in good to excellent yields (Scheme 2.2-68) [107]. The RCM products were then transformed to conjugated dienes by SO_2 extrusion by means of cheletropic ring opening and then reacted with dienophiles to afford Diels-Alder products. Cyclic sulfones also underwent clean and high-yielding Ramberg-Bäcklund rearrangement to afford regiospecific cyclic olefins.

Synthesis of cyclic α -thiophosphonates by utilizing transition metal catalysis reactions was recently reported [108]. A sequential $\text{Rh}_2(\text{OAc})_4$ -catalyzed sulfur-ylide rearrangement and ruthenium-benzylidene-catalyzed RCM of the resulting allylic sulfides produced the cyclic α -thiophosphonates in moderate to excellent yields (Scheme 2.2-69). The metathesis of a less-substituted substrate ($\text{R}_1 = \text{H}$) was sluggish and less effective, whereas the metathesis of more-substituted substrates ($\text{R}_1 = \text{CO}_2\text{Me}$ or CO_2^tBu) proceeded smoothly and gave excellent yields. The yield enhancement in the RCM could be attributed to both the Thorpe-Ingold effect of the bulky geminal disubstituted phosphonacetates and the possible shielding effect of the bulky ester groups, which might prevent the lone pairs on the sulfide from poisoning the ruthenium catalyst. Since α -thiophosphonates are potential candidates for pharmaceutical, agricultural, and synthetic agents, this new strategy provides a facile route to their synthesis.

Hanson *Synlett* **2001**, 605

Scheme 2.2-69

Heck *OL* **2002**, 4, 1767

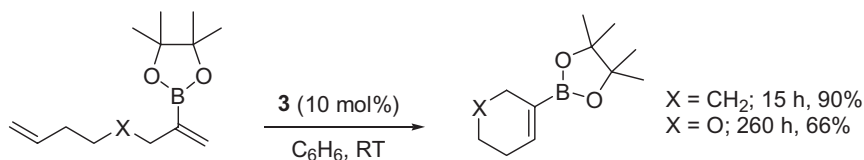
Scheme 2.2-70

Heck investigated the formation of cyclic sulfides, cyclic disulfides, and dithianes via RCM reactions of acyclic diene sulfides, diene disulfides, and diene dithianes using catalyst **4** (Scheme 2.2-70) [109]. RCM reactions with volatile starting materials were run in deuterated solvent to monitor the product formation as well as diene disappearance by NMR experiments.

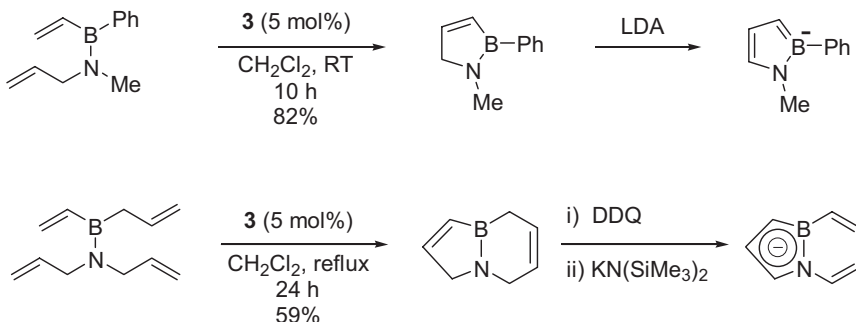
2.2.4.4

B-Heterocycles

Renaud applied RCM to the synthesis of cyclic alkenylboronates (Scheme 2.2-71) [110]. Although non-protected dialkenylboronic acid also was able to react with **3**

Renaud *JACS* **1998**, 120, 7995

Scheme 2.2-71



Ashe III *OL* **2000**, 2, 2089
Organometallics **2002**, 21, 4578

Scheme 2.2-72

to give the cyclic product in moderate yield, the corresponding boronic esters were reacted more efficiently to provide cyclic alkenylboronates, which are potential intermediates in Pd-catalyzed cross-couplings. A series of carbon-, oxygen-, and nitrogen-containing boronate compounds were produced by the RCM.

RCM of appropriate vinyl or allyl aminoboranes produced azaboracycloalkenes in high yields that were subsequently converted to azaborolides or azaborines, which can serve as ligands for transition metal complexation (Scheme 2.2-72) [111]. Ashe later extended this synthesis to the preparation of the fused-ring, di-heteroaromatic 3a,7a-azaborindenyl anion [112].

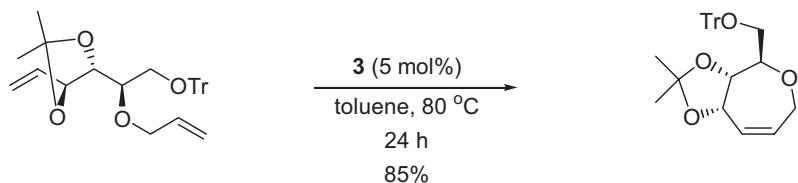
2.2.5

Synthesis of Cyclic Ethers

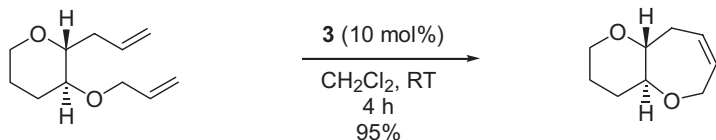
2.2.5.1

Mono- and Bicyclic Ethers

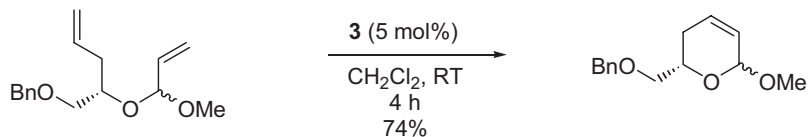
Polycyclic ether antibiotics have been the subject of intense study due to their interesting architectural complex structures, their potent biological profiles, and the synthetic challenges in forming these rings. Since cyclic ether components

Boom *TL* **1998**, 39, 3025

Scheme 2.2-73

Martin *TL* **1997**, 38, 6299
JOC **1999**, 64, 4798

Scheme 2.2-74

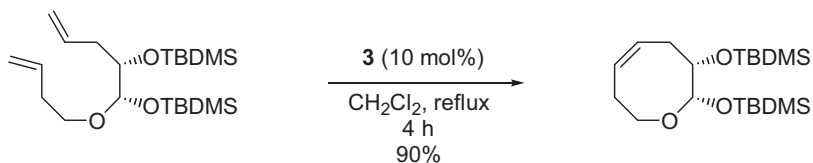
Rutjes *Synlett* **1998**, 192

Scheme 2.2-75

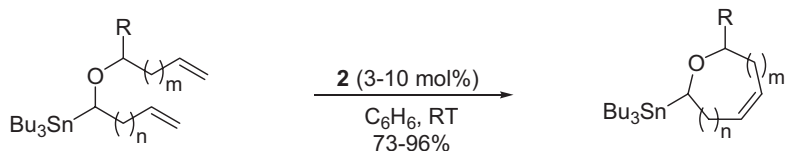
are abundant in natural products, numerous approaches have been disclosed for the synthesis of those cyclic structures. In recent years, much activity has been geared toward forming these rings via ring-closing metathesis of dienes to form oxacycles that are difficult to prepare from other methods. Grubbs showed the first examples of the application of RCM to cyclic ether synthesis [113–115]. Following this report, numerous examples have been published for the formation of cyclic ether rings. Boom developed an efficient route to highly functionalized chiral oxepines [116]. Thus, ring-closing metathesis of linear chiral dienes were cyclized smoothly in the presence of the ruthenium catalyst **3** (Scheme 2.2-73).

Development of routes to *trans*-fused polycyclic ethers has attracted considerable attention from the synthetic community due to the interesting biological activity of these compounds and to the challenges of formation of oxacycles with defined relative stereochemistry. RCM of monocyclic diethers with **3** afforded bicyclic ethers with *trans* relationships (Scheme 2.2-74) [117, 118].

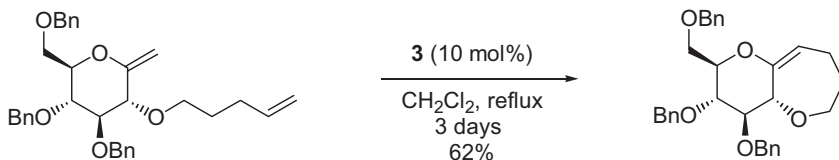
An efficient metathesis route to 2-substituted dihydropyrans from acetals has been reported (Scheme 2.2-75) [119]. Oxacarbenium ion-mediated coupling reactions with allyltrimethylsilane or trimethylsilyl cyanide of the ring-closed products led to 2-substituted dihydropyrans.

Taylor *TL* **1999**, 39, 4267

Scheme 2.2-76

Linderman *JACS* **1997**, 119, 6919

Scheme 2.2-77

Langlois *TL* **1999**, 40, 4801

Scheme 2.2-78

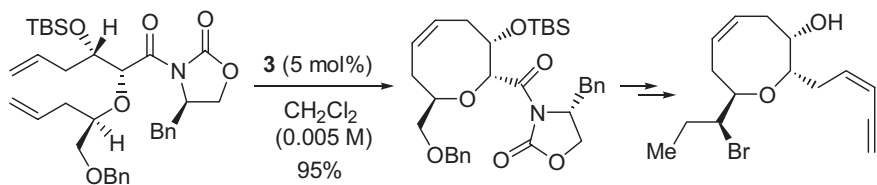
Taylor applied the ruthenium catalyst **3** to dienyl ether to afford 8-membered oxocane in excellent yield during his synthesis of laureatin (Scheme 2.2-76) [120].

The use of tributylstannyl moiety as a further functionalized group that has the additional role of effecting a conformational bias allows the synthesis of an 8-membered oxacyclic ring via RCM [121]. RCM of dienes with **2** led to 8-membered α -(trialkyl)stannyl-substituted cyclic ethers in good yields (Scheme 2.2-77). The stannyl group underwent further transmetalation.

Methylene glucose derivatives were easily converted into C-glycosylidene compounds in the presence of **3** (Scheme 2.2-78) [122].

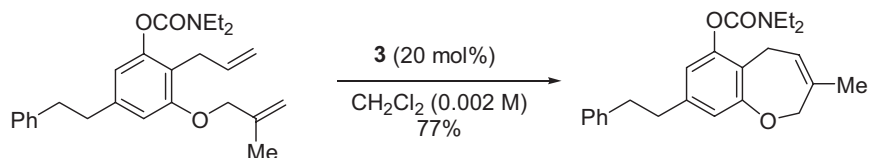
Crimmins elegantly demonstrated the high utility of RCM for the formation of 8-membered rings during syntheses of prelaureatin and its closely related compounds bearing in common 8-membered ether cores (Scheme 2.2-79) [123, 124]. The ring formation was carried out at high dilution in remarkable yields and with no detectable dimerization.

Snieckus utilized RCM methodology for the construction of benzannulated oxygen heterocycles [125]. Dialkenyl benzenes were efficiently converted into benzo-



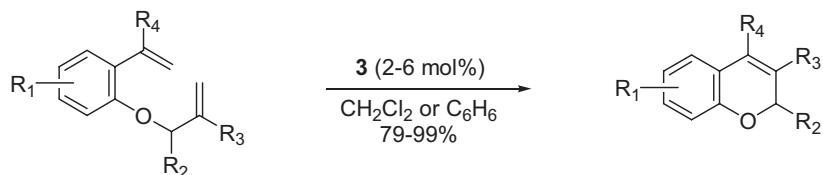
Crimmins *JACS* **1999**, 121, 5653
JACS **2000**, 122, 5473

Scheme 2.2-79



Snieckus *JOC* **1998**, 63, 2808

Scheme 2.2-80



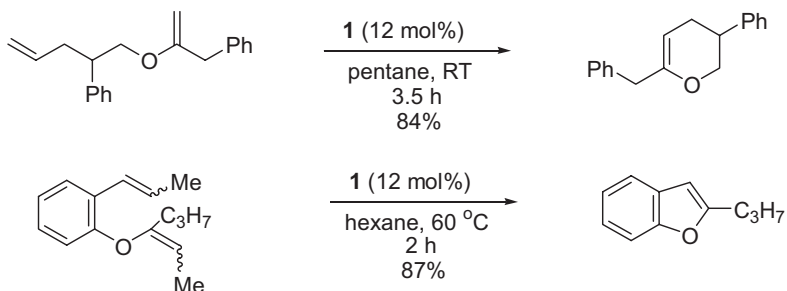
Grubbs *JOC* **1998**, 63, 8664

Scheme 2.2-81

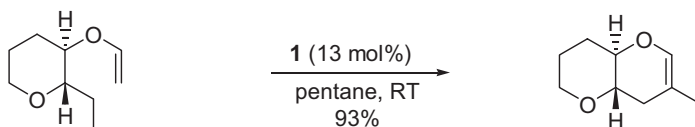
xepine derivatives by the action of **3** (Scheme 2.2-80). This type of compound is a core structure of some natural products such as radulanin or helianane.

An efficient method for the formation of chromenes (2H-benzopyran derivatives) has been described (Scheme 2.2-81) [126]. Styrenyl allyl ether dienes were easily prepared from salicylaldehydes in a one-pot reaction, and the cyclization reactions proceeded in excellent yields in the presence of **3**. A variety of electronically and sterically different substituents were introduced at the varying positions on the chromene framework. Of particular interest is the tolerance of the ruthenium catalyst **3** to both aryl amine and nitro substituents.

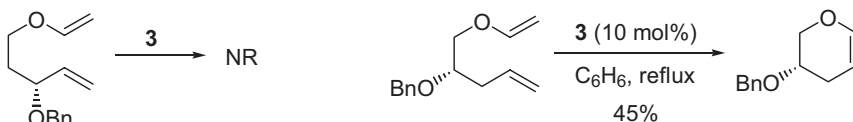
Vinyl ethers have been regarded in general as poor substrates for the ruthenium-based metathesis; therefore, in those cases more reactive molybdenum catalysts are required. It has been assumed that the carbenes formed by the rapid reaction of vinyl ethers with the ruthenium complexes are unreactive for further metathesis reactions. For example, as shown in Scheme 2.2-82, vinyl ether substrates cleanly cyclized to the dihydropyrans when treated with **1** in good yields,

Grubbs *JOC* **1994**, 59, 4029

Scheme 2.2-82

Clark *TL* **1997**, 38, 123

Scheme 2.2-83

Sturino *TL* **1998**, 39, 9623

Scheme 2.2-84

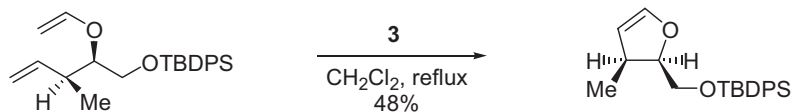
whereas the vinyl ether substrates failed to provide any of the corresponding cyclic enol ethers with ruthenium catalysts such as **2** or **3** [127].

Clark reported successful ring-closing reactions of substrates having enol ether [128, 129]. Molybdenum catalyst was effective for the formation of fused bicyclic pyran systems with remarkable efficiency (Scheme 2.2-83).

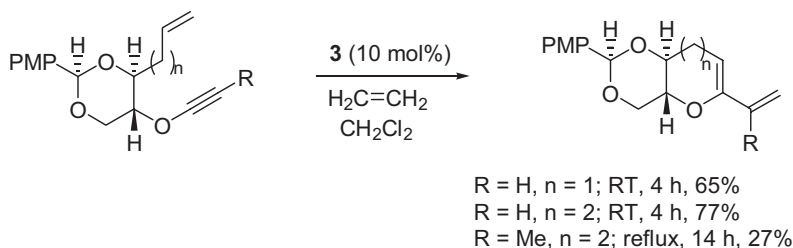
In contrast, some exceptional examples have been recently disclosed by several groups, in which certain vinyl ethers do undergo ring-closing metathesis with the ruthenium catalysts. For example, whereas vinyl ethers having allylic alkoxy substituents were still unreactive with **3**, ring closure of other substrates proceeded smoothly to afford dihydropyrans (Scheme 2.2-84) [130].

Williams utilized an RCM reaction for the formation of a *cis*-disubstituted dihydrofuran from *syn*-homoallyl vinyl ether (Scheme 2.2-85) [131]. Cyclization with **3** gave the 4,5-dihydrofuran as a single product in moderate yield.

Clark applied the enyne ring-closing metathesis of alkynyl ethers for the formation of alkenyl-substituted cyclic enol ethers, which are common subunits found

Williams *ACIEE* **2000**, 39, 4612

Scheme 2.2-85

Clark *CC* **1998**, 2629

Scheme 2.2-86

in brevetoxins and ciguatoxins (Scheme 2.2-86) [132]. Interestingly, the terminal alkynyl ether (R = H, n = 1) underwent efficient cyclization, although a higher yield was obtained upon reaction of the non-terminal alkynyl substrate (R = Me, n = 1). The enyne metathesis to produce 7-membered cyclic enol ethers proved to be less successful than those to give the alkenyl-substituted dihydropyrans. The pendant vinyl group of the products can provide scope for construction of additional cyclic ether by a subsequent metathesis reaction.

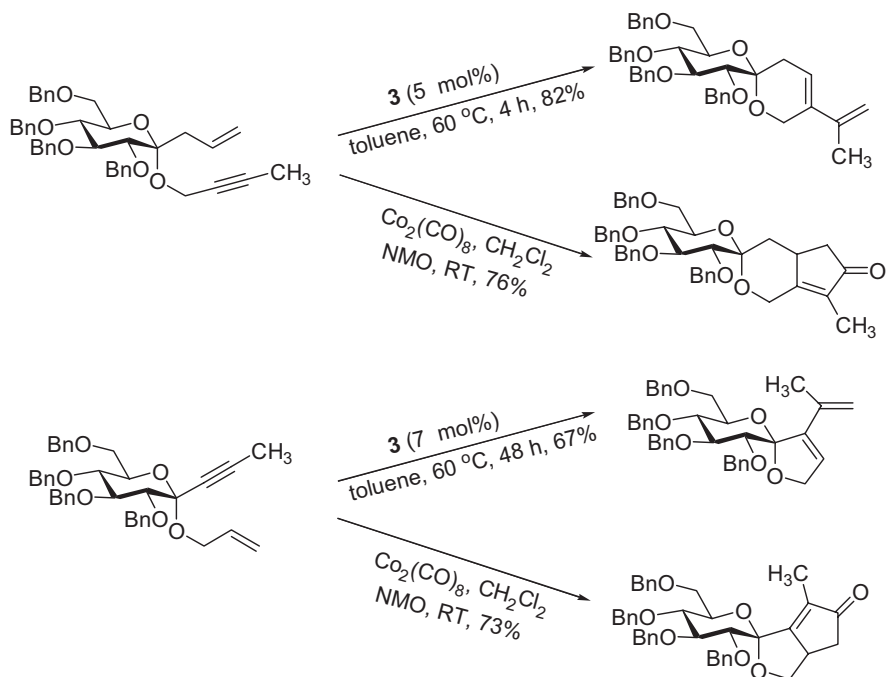
Synthesis of highly functionalized carbohydrate-derived spirocyclic ethers by RCM of ketoglycosidic enynes has been reported [133]. When Pauson-Khand cyclization conditions were applied to the same enynes, the corresponding cyclopentenone spiroacetals were synthesized instead (Scheme 2.2-87).

2.2.5.2

Polycyclic Ethers

Several polycyclic ethers have been isolated and synthesized for their structural novelty and biological properties since the discovery of brevetoxin B in 1981 [134]. Ciguatoxins are a burgeoning family of polycyclic ethers of marine origin having potent biological activities [135]. Due to their fascinating molecular architectures and inherent synthetic challenges, numerous synthetic pathways have been disclosed especially with regard to ring synthesis and stereocontrol (Figure 2.2-3).

RCM has proven to be a key step in the synthesis of fragments of ciguatoxins. Hirama applied the RCM reaction to the tricyclic ether system of ciguatoxin to afford tetracyclic ether in respectable yield (Scheme 2.2-88) [136].



Boom *EJOC* **2000**, 873

Scheme 2.2-87

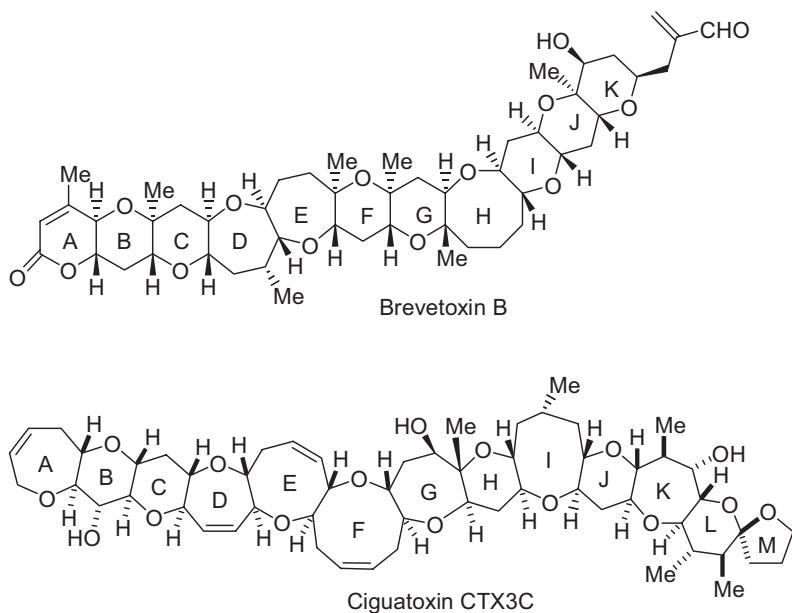
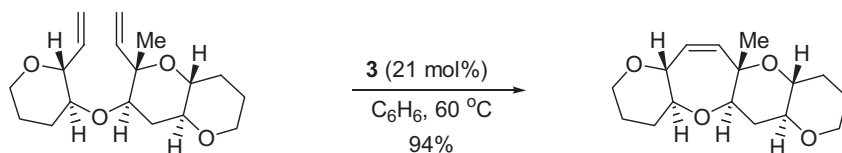
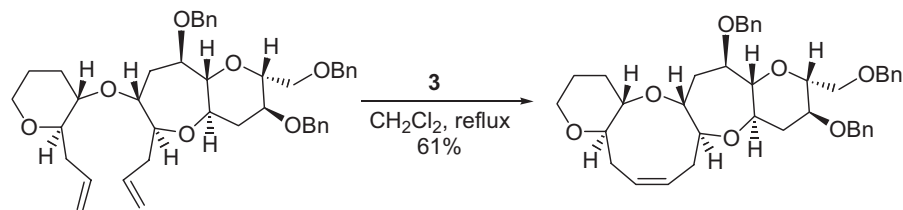


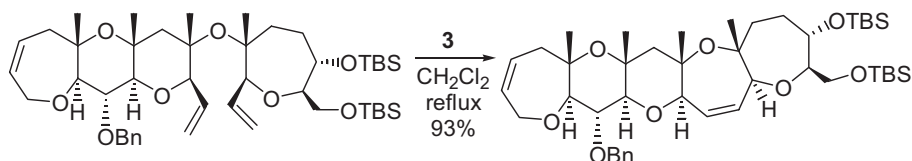
Fig. 2.2-3. Structures of brevetoxin B and ciguatoxin CTX3C.

Hirama CC **1998**, 1041

Scheme 2.2-88

Sasaki TL **1999**, 40, 1337

Scheme 2.2-89

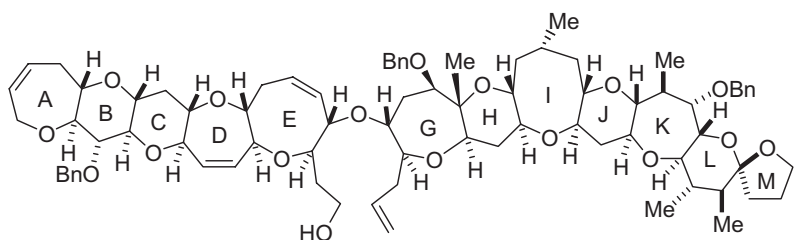
Hirama CC **1999**, 1063

Scheme 2.2-90

Similarly, dienes of tricyclic ethers were smoothly cyclized to give 8- and 9-membered tetracyclic ethers in moderate yields (Scheme 2.2-89) [137]. The tetracyclic products are the FGH ring fragment of ciguatoxin.

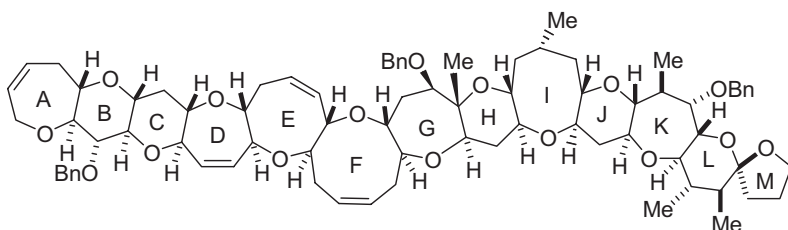
RCM of tetracyclic ether furnished the fully functionalized pentacyclic ABCDE ring framework of ciguatoxin (Scheme 2.2-90) [138].

Recently, Hirama completed the total synthesis of ciguatoxin CTX3C by using the chemoselective RCM reaction as a key tactic. The natural product, ciguatoxin CTX3C, is the largest molecule (3 nm long) synthesized to date. The critical chemoselective RCM in the presence of preexisting disubstituted double bonds was successfully achieved in the final stage of the total synthesis of this highly complicated natural product [139]. The substrate was prepared from the alcohol via a two-step sequence, an oxidation followed by a Wittig reaction. The RCM reaction of the penta-olefinic product with catalyst **3** in refluxing dichloromethane to close the F ring afforded the fully protected ciguatoxin CTX3C in 60% yield in three steps. Notably, the undesired ROMP reaction of the olefins did not occur during the



i) $\text{SO}_3\cdot\text{Py}$, Et_3N , DMSO
 II) $\text{Ph}_3\text{PCH}_2\text{Br}$, NaHMDS

iii) **3** (20 mol%), CH_2Cl_2 , 40 °C, 8 h
 60% for three steps



Hirama *Science* **2001**, 294, 1904

Scheme 2.2-91

reaction (Scheme 2.2-91). The use of RCM in the final steps of the major synthesis clearly demonstrates the confidence of synthetic chemists in the utility of metathesis reactions.

Yamamoto disclosed the use of both catalysts **3** and **5** for the formation of 7- and 8-membered cyclic ethers in the convergent synthesis of the CDEF ring system of brevetoxin B (Scheme 2.2-92) [140, 141].

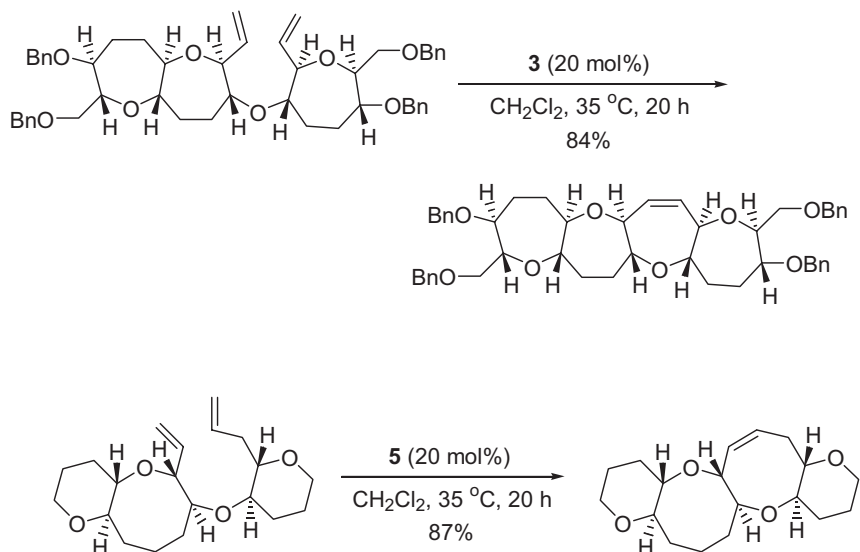
2.2.6

Applications to *N*-Heterocycles and Peptide Chemistry

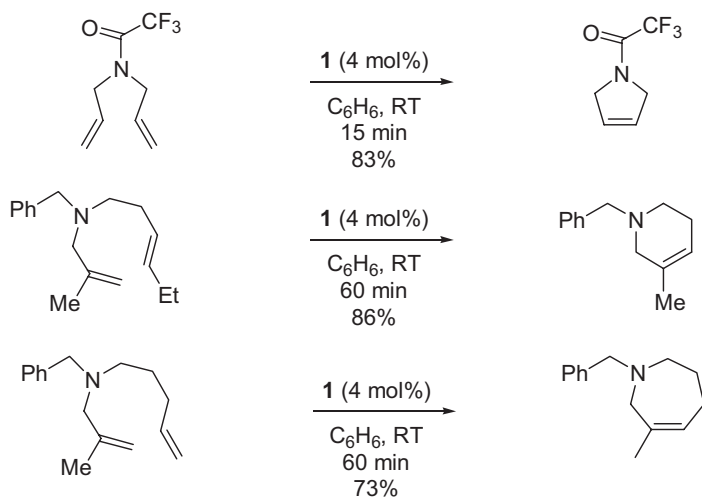
2.2.6.1

N-Heterocycles

Due to the high efficiency of RCM for the formation of cyclic compounds, RCM recently has been employed as a powerful tool in the area of nitrogen-containing heterocycles as well as peptide and peptidomimetics research. Grubbs showed the first example in which alkenyl tertiary amines converted smoothly into *N*-heterocycles with the Mo catalyst (Scheme 2.2-93) [113].

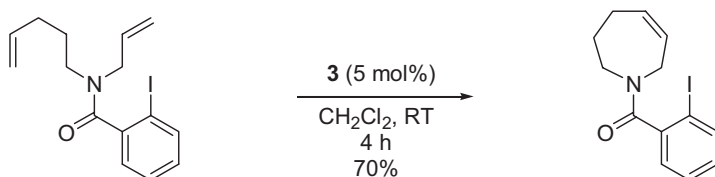
Yamamoto *JACS* **2002**, *124*, 3562

Scheme 2.2-92

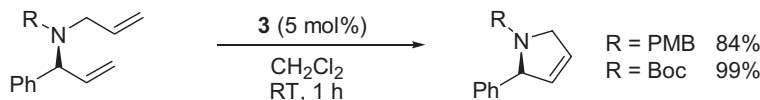
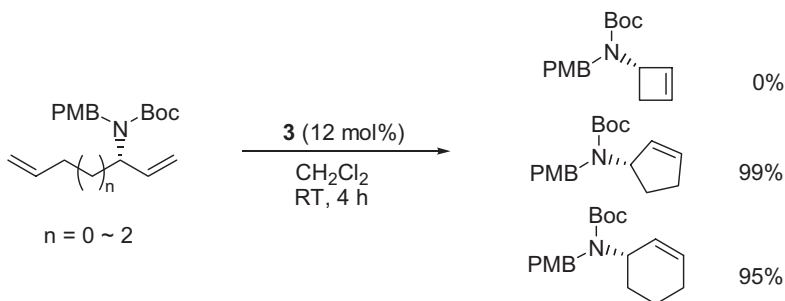
Grubbs *JACS* **1992**, *114*, 7324

Scheme 2.2-93

Grigg exploited sequential and cascade reactions in which the olefin-metathesis step played a key role [142]. Halogen-substituted amide or sulfonamide precursors underwent smooth cyclization with the ruthenium catalyst **3** (Scheme 2.2-94). The cyclic products were converted to tricyclic compounds by subsequent intramolecular Heck reactions.

Grigg *TL* **1998**, 39, 4139

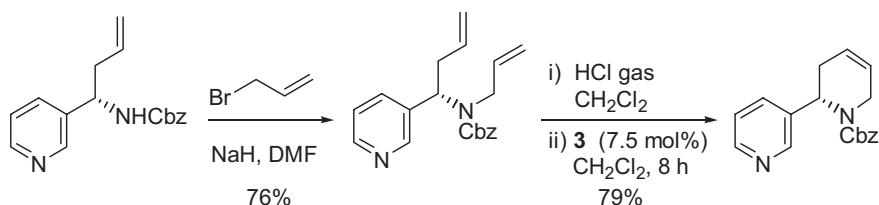
Scheme 2.2-94

Riera *JOC* **2002**, 67, 6896

Scheme 2.2-95

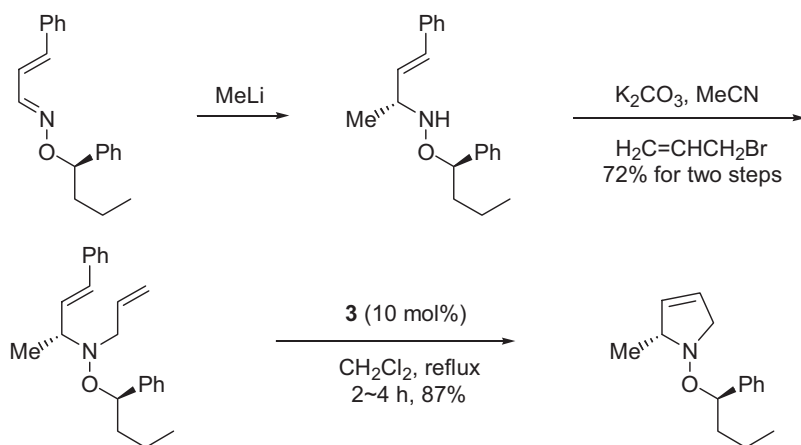
Polyhydroxylated cyclic amines, which can be obtained by dihydroxylation of unsaturated cyclic amines, are widespread in nature and exhibit interesting bioactivities. Riera reported efficient synthesis of unsaturated cyclic amines via RCM with two types of bis-allylamines, so-called fully protected amines as well as monoprotected amines (Scheme 2.2-95) [143].

Lebreton synthesized piperidine alkaloids in enantiomerically pure forms from a diethylenic amine using RCM as the key step (Scheme 2.2-96) [144]. The RCM reaction of the protected *N*-allylamine with catalyst **3** to afford *N*-heterocyclic compounds failed, presumably due to the interference of the pyridine nitrogen with the catalytic cycle of ruthenium by coordinating to the metal. This problem was easily solved by protonating the pyridine nitrogen with dry HCl to block the nitrogen functionality. The hydrochloride pyridinium salt was then smoothly cyclized with **3** (5 mol%, 4 h and then 2.5 mol%, 4 h) to furnish the piperidine alkaloid precursor in good yield.



Lebreton *JOC* **2001**, 66, 6305

Scheme 2.2-96



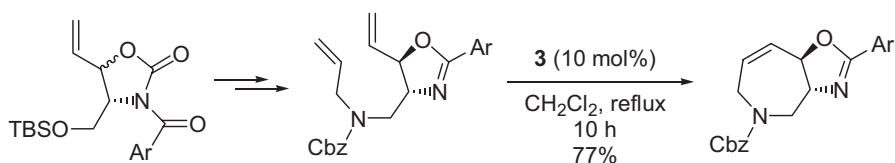
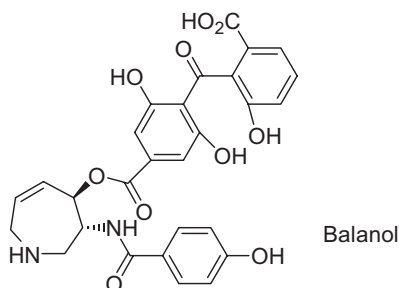
Moody *JCSPT1* **2002**, 2378

Scheme 2.2-97

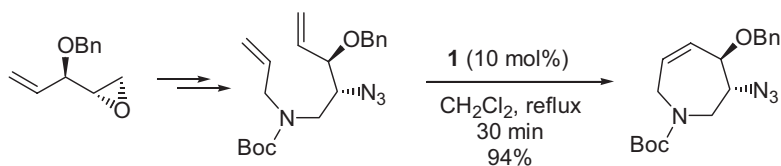
Moody disclosed an asymmetric synthesis of 2-substituted 5- to 8-membered nitrogen heterocycles via organometallic addition to a chiral oxime ether followed by RCM (Scheme 2.2-97) [145].

Balanol, first isolated in 1993 and a potent inhibitor of human protein kinase C, has attracted much attention from the synthetic community [146]. The 7-membered heterocyclic core of balanol was recognized as a testing ground for probing the utility of RCM. Cook prepared the diene as an RCM substrate starting from D-serine in nine steps, and the key ring-closure reaction was carried out with **3** to provide the 7-membered N-heterocycle in respectable yield (Scheme 2.2-98) [147].

Fürstner demonstrated another elegantly efficient RCM-based synthesis in the approach to balanol (Scheme 2.2-99) [148]. Starting from vinyl epoxy ether, the RCM substrates were easily prepared in a rather short steps. RCM reactions in which the dienes contained either a free hydroxyl group or an azide group were highly efficient, depending on the catalysts employed. While RCM of the diene

Cook *OL* **1999**, 1, 615

Scheme 2.2-98

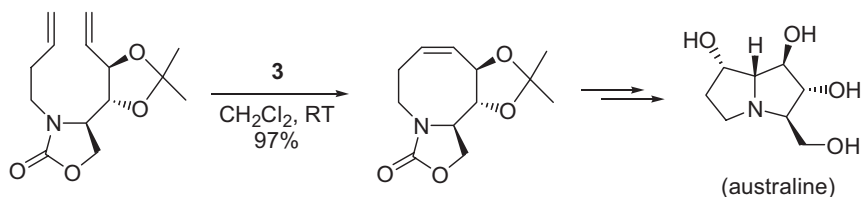
Füerstner *JOC* **2000**, 65, 1738

Scheme 2.2-99

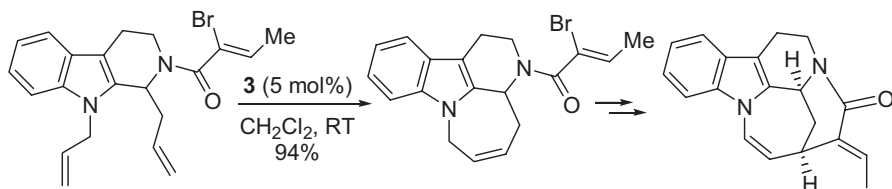
bearing a free hydroxyl substituent was best effected by ruthenium catalysts (69–88%), those catalysts did not convert the azide substrate into the desired cycloalkene even at high temperature. In contrast, the higher reactivity of the molybdenum catalyst **1** allowed the reaction to occur at lower temperature to afford the product in excellent yields.

White employed ring-closing metathesis as a key step during his synthesis of australine [149]. Azacyclooctene product was obtained in excellent yield in the presence of **3** (Scheme 2.2-100).

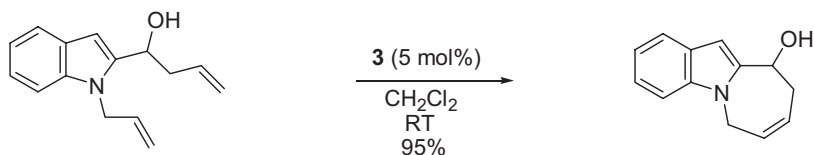
Rawal utilized the RCM reaction of diallyl tricyclic substrate to afford tetracyclic product (Scheme 2.2-101) [150]. Intramolecular Heck cyclization of the resulting

White *JACS* **1998**, 120, 7359

Scheme 2.2-100

Rawal *JOC* **1998**, 63, 9146

Scheme 2.2-101

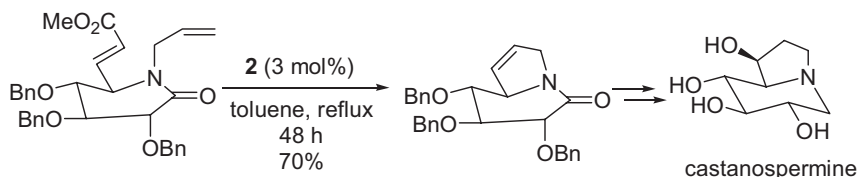
Perez-Castells *TL* **2002**, 43, 4765

Scheme 2.2-102

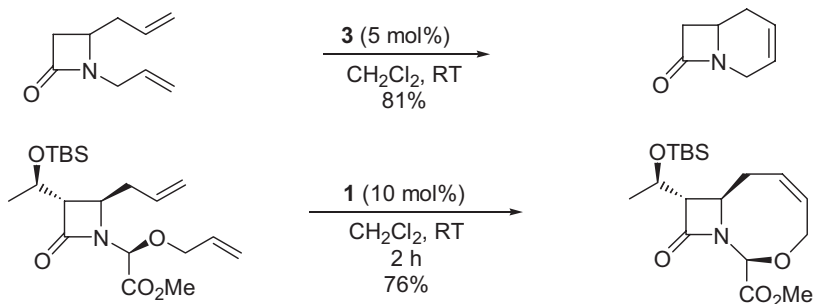
compound gave pentacyclic amide in a stereoselective manner. These steps represented a general, stereocontrolled route to the geissoschizine and akagerine alkaloid family of natural products.

The RCM reaction with a series of 1,2-disubstituted indoles afforded interesting tricyclic intermediates in the synthesis of alkaloids (Scheme 2.2-102) [151]. The combination of methylene chloride and catalyst **3** as the RCM reaction condition leads to indole tricyclic derivatives in excellent yields.

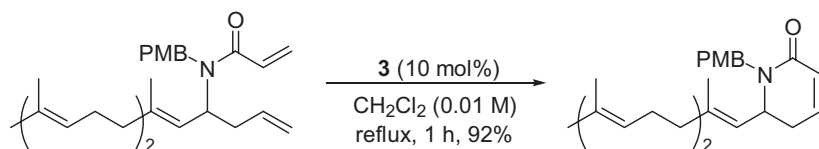
Pandit explored the applications of RCM of dienes appended to polysubstituted pyrrolidinones and piperidinones [152]. These studies expanded upon an early report of a concise synthesis of castanospermine, a member of a large family of polyhydroxylated alkaloids. Cyclization of the diene afforded the bicyclic lactam in good yield in the presence of **2**, which demonstrated that α,β -unsaturated esters may be suitable substrates for metathesis (Scheme 2.2-103).

Pandit *TL* **1996**, 37, 547

Scheme 2.2-103

Barrett *CC* **1996**, 2231
CC **1997**, 155
JOC **1998**, 63, 7893

Scheme 2.2-104

Wiemer *JOC* **2002**, 67, 5701

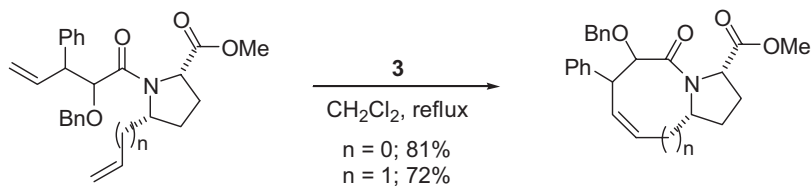
Scheme 2.2-105

2.2.6.2

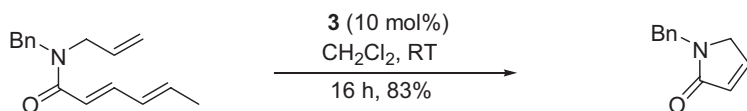
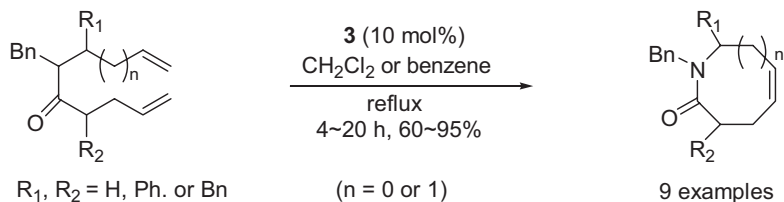
Small and Medium-Sized Lactams

Olefin metathesis has been shown to be an effective process for the functionalization of monocyclic β -lactam and for the formation of bicyclic β -lactams via the ring closure of monocyclic diene precursors (Scheme 2.2-104) [153–156].

Wiemer recently described the use of RCM during the synthesis of an α -phosphono lactam and a lactone derivative of farnesol (Scheme 2.2-105) [157]. The

Moeller *TL* **1998**, 4639

Scheme 2.2-106

Guibe *Synlett* **2001**, 37

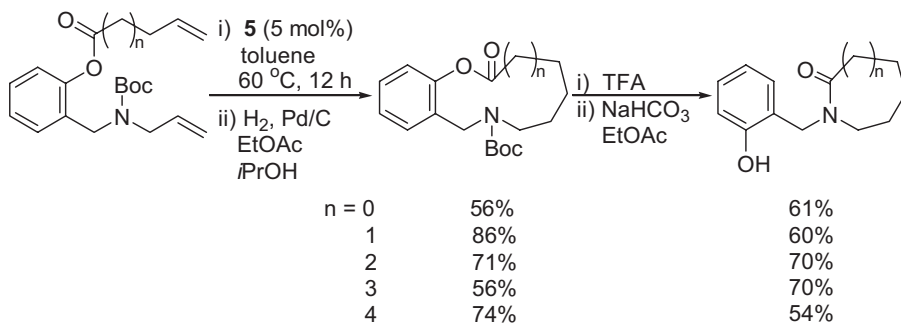
Scheme 2.2-107

conjugated δ -lactam was formed in excellent yield from the PMB-protected amide via RCM.

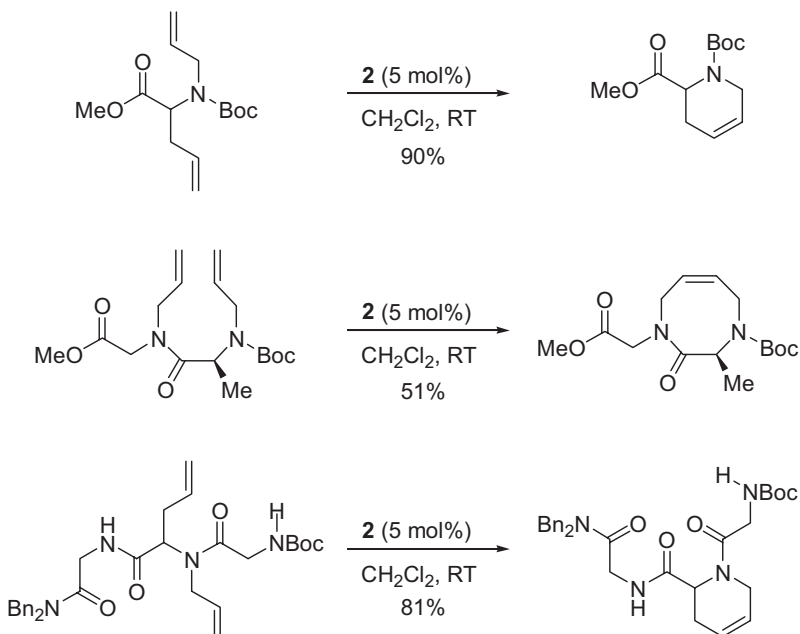
Synthesis of a 7-membered lactam having conformationally restricted thyro-liberin analogues was described by Moeller (Scheme 2.2-106) [158]. This RCM-based approach also allowed preparation of bicyclic lactams having a variety of different ring sizes and different R groups β to the lactam carbonyl.

Guibé successfully synthesized 5- to 8-membered unsaturated lactams through RCM of unsaturated tertiary amides, which ensured sufficient proportion of the rotamer with the two ethylenic appendages *syn* to each other for efficient RCM (Scheme 2.2-107) [159].

Maarseveen reported an interesting strategy with regard to the synthesis of medium-sized lactams utilizing RCM, followed by a templated transannular aminolysis reaction to give 7- to 10-membered lactams. A versatile RCM process was chosen for the tethered cyclization step. Correct spatial positioning of the secondary amine combined with carbonyl functional groups for the transannular ring-contraction reaction afforded the desired target lactams in good yields (Scheme 2.2-108) [160].

Maarseveen *OL* **2002**, *4*, 2673

Scheme 2.2-108

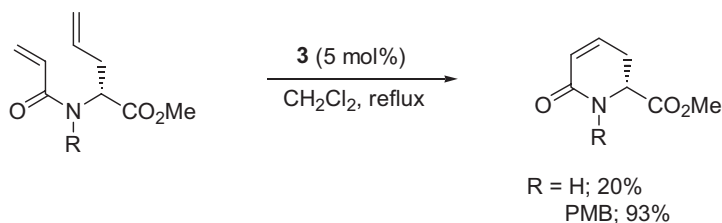
Grubbs *JACS* **1995**, *117*, 5855

Scheme 2.2-109

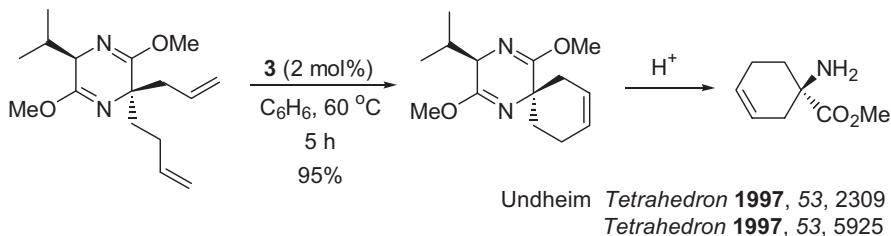
2.2.6.3

Cyclic Amino Acids, Peptides, and Peptidomimetics

A number of applications of RCM have also been disclosed for the synthesis of cyclic amino acids containing various ring sizes, and this strategy was subsequently introduced into peptides (Scheme 2.2-109) [161, 162]. While 6-membered rings of

Rutjes *TL* **1997**, 38, 677

Scheme 2.2-110



Scheme 2.2-111

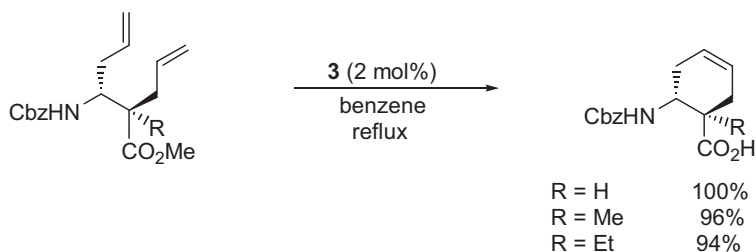
amino acids were readily formed with the ruthenium catalyst **2** in excellent yields, general efficiency for 7- or 8-membered derivatives was lower under normal conditions; therefore, highly dilute concentrations were required to obtain acceptable yields in those cases. Tripeptidic substrate was efficiently cyclized, which demonstrates sufficient tolerance of the catalytic conditions even for unprotected amide NH groups.

Highly functionalized 6- and 7-membered amino esters and acrylic amides were prepared by the action of **3** from the corresponding amino-acid-derived dienes (Scheme 2.2-110) [163]. The yields for the ring closure were varied upon the presence of a protecting group of amidic NH bond.

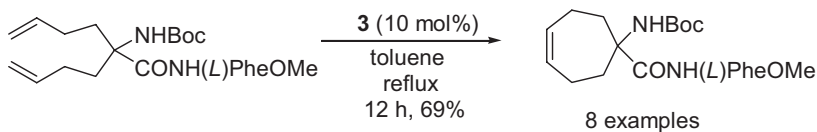
Stereoselective synthesis of rigidified α -amino acids where the α -carbon of the amino acids is incorporated into 5-, 6-, or 7-membered rings has been described by Undheim (Scheme 2.2-111) [164, 165]. RCM of the geminal diolefins was efficiently performed by the Ru catalyst **3** (2 mol%) in an aromatic solvent. The cyclization appears to be sensitive to the steric interactions between the catalyst and the substituents of the substrates. Hydrolysis of the spiro products under mildly acidic conditions provided a novel type of cyclic amino ester.

A versatile RCM approach also allowed the preparation of *cis* and *trans* cyclic β -amino acids that were both α -free and α -substituted derivatives. The ruthenium catalyst **3** afforded the cyclohexenyl-based β -amino acid as a single diastereomer in excellent yield (Scheme 2.2-112) [166].

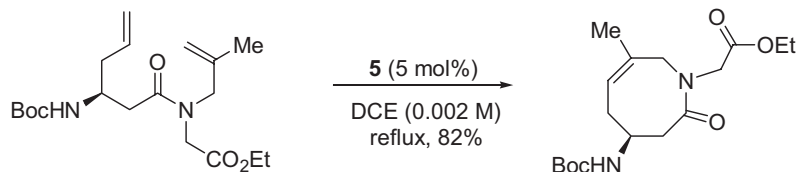
A simple method for the preparation of cyclic peptide derivatives was reported using the RCM reaction in a post-translational-type peptide-modification reaction to form compounds suitable for both peptidomimetic and combinatorial chemistry applications (Scheme 2.2-113) [167].

Abell *OL* **2002**, 4, 3663

Scheme 2.2-112

Kotha *BMCL* **2001**, 11, 1421

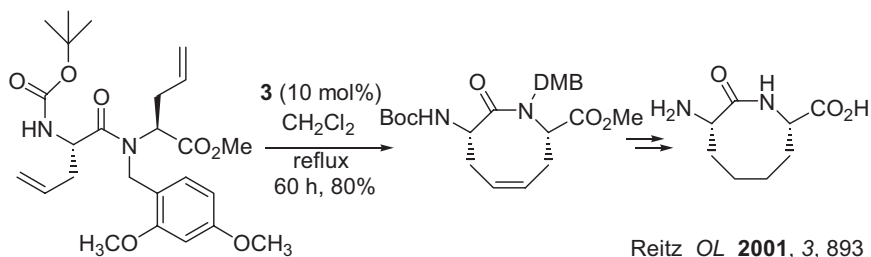
Scheme 2.2-113

Gmeiner *Synlett* **2002**, 1014

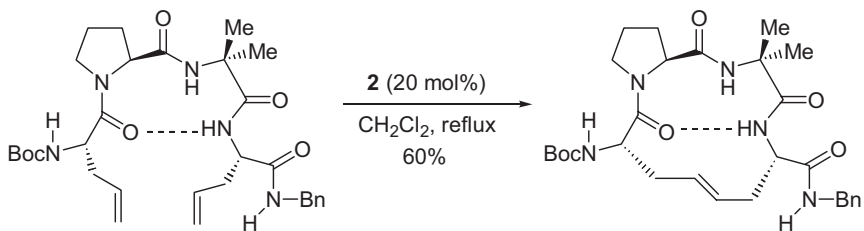
Scheme 2.2-114

The complexity of molecular recognition processes between peptide ligands and bioreceptors provides a motivation for the study of constrained peptides. The incorporation of peptide backbones into cyclic olefins should constrain the backbone of amino acids. Lactam-bridged peptide mimics were designed and synthesized using RCM as the key reaction step to afford conformationally restricted β -amino acid analogues. The RCM reaction was run in DCE at reflux (81 °C), since it was known that elevated temperatures facilitate ring closure to medium-sized cyclic compounds (Scheme 2.2-114) [168].

The most common feature in cyclic peptides and proteins is the S–S disulfide unit derived from cystine. Reitz efficiently synthesized an 8-membered cyclic pseudo-dipeptide using RCM to increase the chemical stability of a biologically active cyclic dipeptide, an oxidized Cys-Cys 8-membered ring. The disulfide functionality was replaced by two carbon atoms in the peptidomimetic. RCM was promoted by the appropriate protection of the amide nitrogen with a 2,4-



Scheme 2.2-115

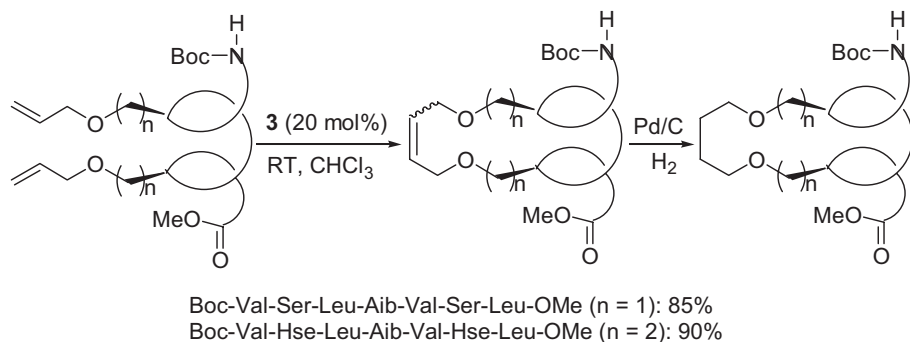
Grubbs *JACS* **1996**, *118*, 9606

Scheme 2.2-116

dimethoxybenzyl group, thereby allowing the required *cis* diallylglycine amide rotamer for intramolecular reaction (Scheme 2.2-115) [169].

Cyclization of peptides is a way to reduce the flexibility of the moiety and to increase the affinity of the peptides towards a receptor. Such peptide congeners are interesting because they serve as unusual templates for pharmacophore recognition at biological targets and can mimic natural secondary turn structures. Among several fundamental motifs utilized by nature for protein assembly, reverse turns, including β -turns, have been identified as playing critical roles in molecular recognition. The β -turn is therefore an attractive motif for intervention by conformationally constrained peptidomimetic scaffolds. The first example of the formation of a dicarba analogue of a disulfide β -turn structure was disclosed by Grubbs (Scheme 2.2-116) [161, 162]. Initially, it was thought that preexisting conformational restrictions such as a Pro-Aib sequence in the peptide backbone would be necessary to induce RCM. However, the success of the cyclization shown in Scheme 2.2-116 demonstrates that this may not strictly be the case. Reaction of a tetrapeptide, in which both the Pro and Aib residues were replaced with leucine, afforded the 14-membered cyclic tetrapeptide in impressive yield by the action of 2.

An interesting example of the use of RCM to give peptidic supramolecular structures was the preparation of helical polypeptides (Scheme 2.2-117) [170, 171]. Heptapeptides, in which the *i* and (*i* + 4) residues of the peptides were linked, were obtained by the RCM of the corresponding diolefinic precursors. The relative ease of introducing C–C bonds into peptide secondary structures by RCM and the



Grubbs *ACIEE* **1998**, 37, 3281
JOC **2001**, 66, 5291

Scheme 2.2-117

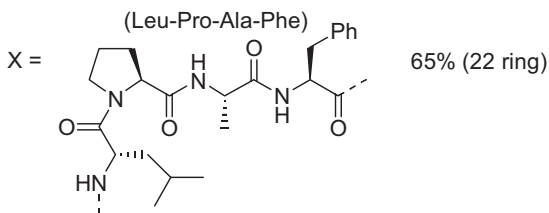
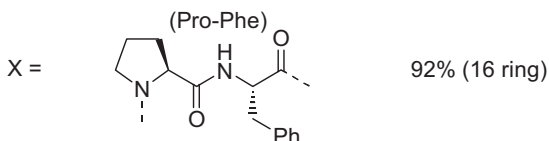
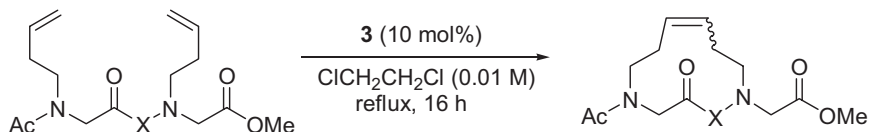
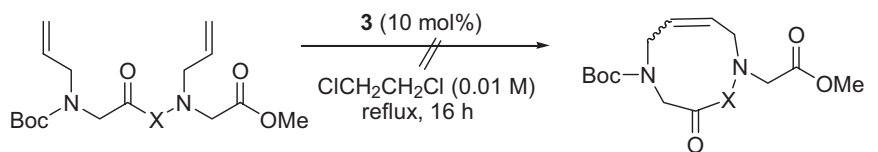
predicted metabolic stability of the bonds render olefin metathesis an exceptional methodology for the synthesis of rigidified peptide architectures.

Bis-*N*-allyl and bis-*N*-homoallyl peptides were effected by the RCM reaction as part of a “backbone-to-backbone” cyclization strategy for the synthesis of cyclic peptides (Scheme 2.2-118) [172–175]. With bis-*N*-allyl peptides bearing *N*-Boc and a Me ester C terminus, no cyclized products were isolated regardless of ring sizes (11-, 14-, 17-, and 20-membered rings). However, when both alkenes were tethered to the peptide backbone with a chain containing an additional methylene and *N*-acetyl *N*-terminus protection, the reaction generally worked well to give macrocyclic olefin with 13-, 16-, 19-, and 22-membered peptides.

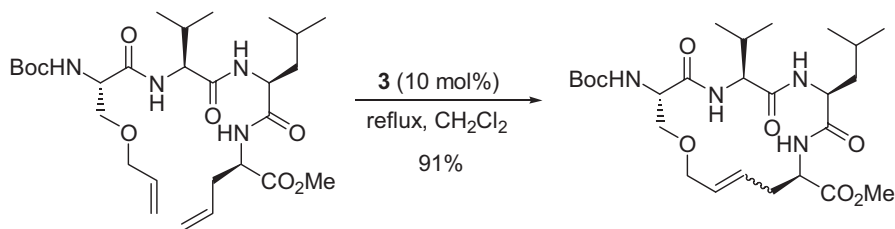
From the studies of Kazmaier, it turned out that proline residue was not a conformationally required part in the cyclization of diolefinic peptides (Scheme 2.2-119) [176]. Moreover, it was claimed that ring size played a major role in the success of the cyclization and that the amino acid sequence and conformational issues were less important, at least for peptides with larger than 14-membered ring sizes.

Ripka described the synthesis of novel cyclic inhibitors of aspartic protease using RCM (Scheme 2.2-120) [177]. Dialkenyl precursors were efficiently converted with the treatment of **3** to afford flexible, non-conformationally constrained tripeptides in excellent yield. The cyclic peptides showed micro- to nanomolar inhibition of *Rhizopus chinensis* pepsin.

Katzenellenbogen employed RCM as a part of his studies on a type I dipeptide structural mimic of protein and peptidic β -turns (Scheme 2.2-121) [178]. Here, the use of RCM on a dipeptide allowed the facile synthesis of the highly constrained 10-membered lactam in six steps. By comparison, a more classic macro-lactamization pathway to this compound required nine steps, and the RCM route had the added advantage of providing access to the (3*S*,10*S*) diastereomer, which was unobtainable by the original route. Conformational analysis of the cyclized lactam indeed showed a type I β -turn structural characteristic.

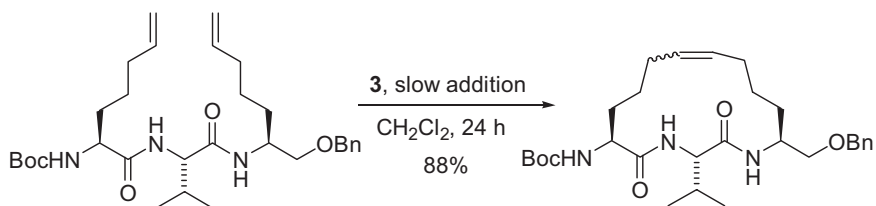
Liskamp *JOC* **2000**, 65, 6187

Scheme 2.2-118

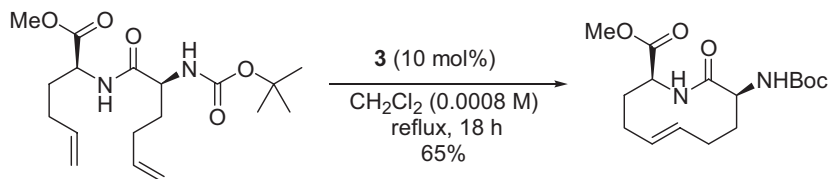
Kazmaier *OL* **1999**, 1, 1763

Scheme 2.2-119

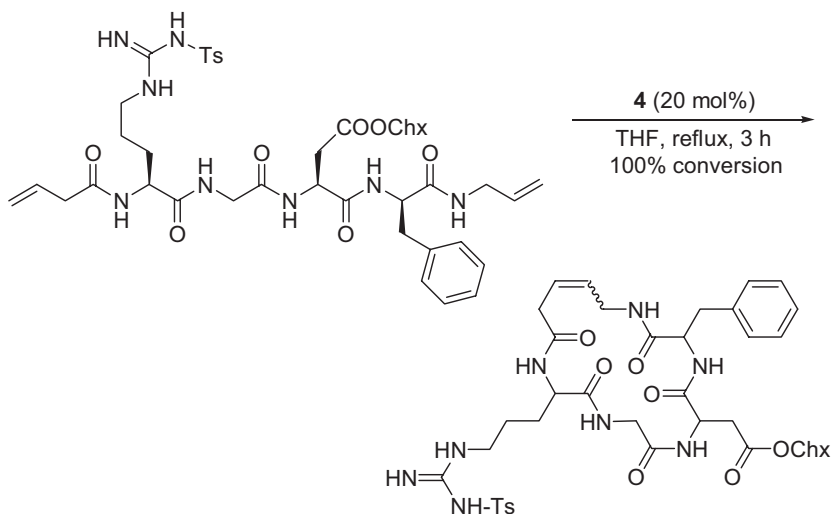
The RCM reaction is a new way of introducing the dehydrocarba surrogate of the peptide bond to establish enzymatically resisting lipophilic isosteric mimics. Lamaty recently disclosed the synthesis of a conformationally restricted cyclic pseudopeptide containing the RGD sequence by RCM using catalyst **4** in tetrahydrofuran (Scheme 2.2-122) [179]. Use of the less popular THF as solvent in RCM for better solubility of the peptide precursor resulted in a quantitative cyclization yield, indicating that the THF oxygen might have interacted with the catalyst

Ripka *Biorganic* **1998**, 357

Scheme 2.2-120

Katzenllnbogen *JACS* **1998**, 4334

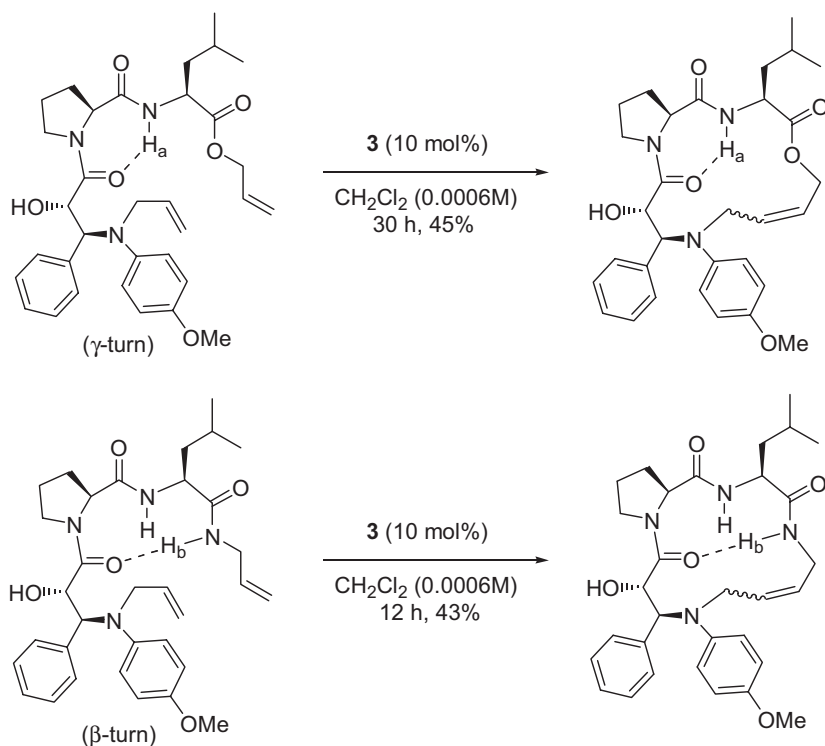
Scheme 2.2-121

Lamaty *TL* **2002**, 43, 3765

Scheme 2.2-122

and released possible unproductive chelates with the functional groups of the peptide.

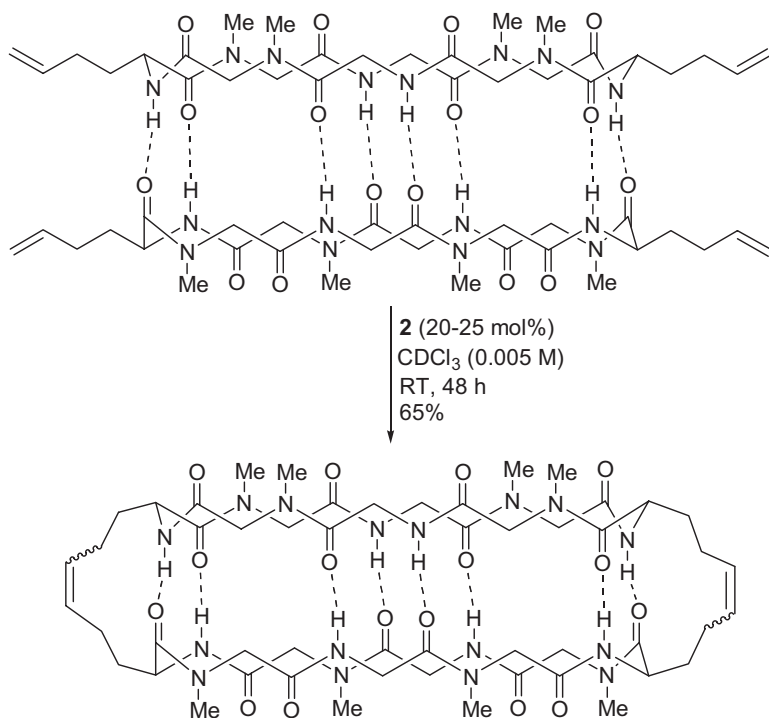
Iqbal recently designed small cyclic peptides based on the concept of restricting the conformational freedom in flexible linear peptides by introducing constraints

Iqbal *JOC* **2002**, 67, 8247

Scheme 2.2-123

in the structures; he then synthesized them via a reverse-turn-induced (γ/β -turn) RCM of linear peptides with the catalyst **3** (Scheme 2.2-123) [180]. The role of the intramolecular 7-membered (γ -turn) or 10-membered (β -turn) hydrogen bond of the linear peptide for RCM was clearly manifested. RCM on the linear peptide that was lacking the intramolecular hydrogen bond did not yield any of the corresponding cyclic peptide. On the other hand, the peptide that existed as a pre-organized structure, presumably due to the presence of the γ - or β -turn by the intramolecular hydrogen bond, proceeded smoothly in the RCM reaction to afford the corresponding cyclic peptide as a mixture of *E:Z* (4:1) isomers. The β -turn appeared to pre-organize the peptide structure more efficiently than the γ -turn and therefore required a relatively shorter reaction period.

Ghadiri elegantly showed that the 8-residue cyclic peptide *cyclo*[-(*L*-Phe-*D*-MeNAla-*L*-Hag-*D*-MeNAla)₂], containing two *L*-homoallylglycine residues, self-assembles to form interconverting H-bonded diastereomer ensembles (Scheme 2.2-124) [181]. It contains two pairs of double bonds in sufficiently close proximity that each pair undergoes RCM by the catalyst **2** to afford a tricyclic cylindrical 38-



Ghadiri *JACS* **1995**, *117*, 12364

Scheme 2.2-124

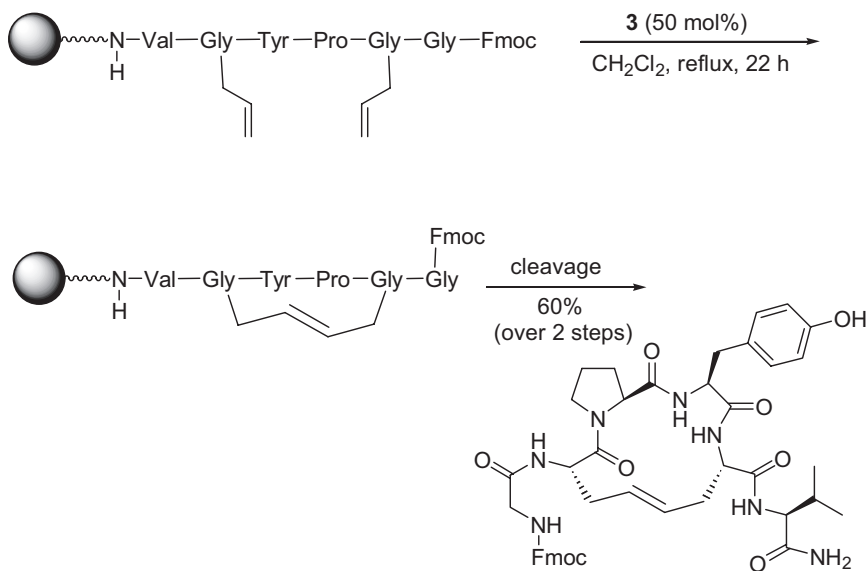
membered ring. This covalent capture strategy may be useful in stabilizing kinetically labile α -helical and β -sheet peptide secondary structures.

The feasibility of performing the RCM on solid-support-bound peptides has been realized (Scheme 2.2-125) [162]. RCM of the diolefinic peptide, prepared by the standard solid-phase peptide synthesis on a Tentagel resin, was effected under metathesis conditions analogous to the solution-phase RCM conditions. Efficiency of the solid-phase reactions was revealed to be analogous to the solution-phase cyclization.

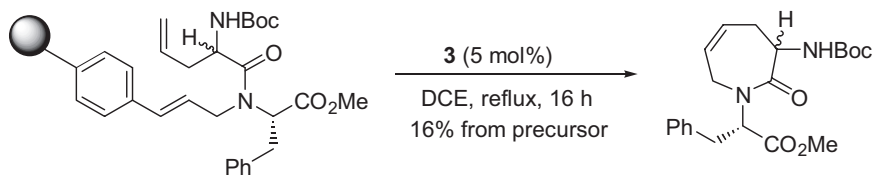
Complementary solid-phase synthesis of the Freidinger lactam class of β -turn mimetics has been developed by Piscopio (Scheme 2.2-126) [182–184]. The lactam was efficiently produced with the treatment of catalyst **3** on the solid-supported diene precursors via a cyclic cleavage pathway.

A method for the synthesis of dimeric peptides has been disclosed based on RCM of solid-supported alkenyl peptide monomers (Scheme 2.2-127) [185]. If the double bonds involved were separated by at least two methylene chains from the amide group, products of good purity could be isolated.

A covalently rigidified octapeptide was prepared through solid-phase RCM for screening of asymmetric peptide catalysts (Scheme 2.2-128) [186]. Cross-linking

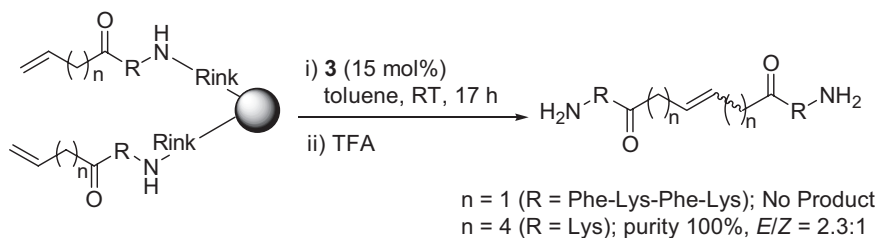
Grubbs *JACS* **1996**, *118*, 9606

Scheme 2.2-125

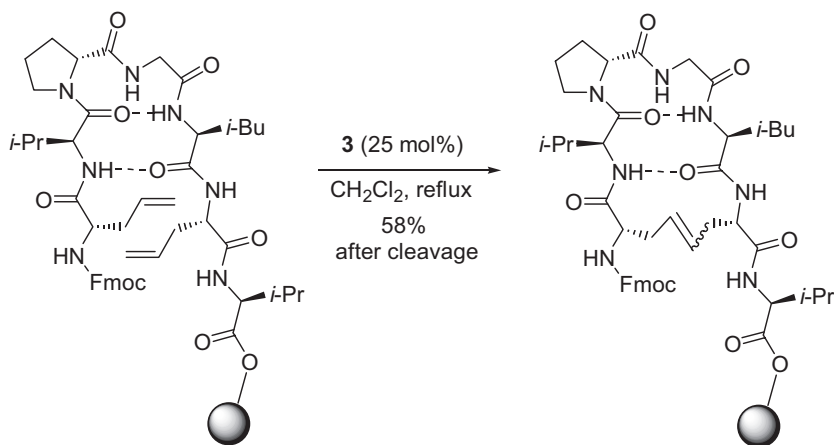


Piscopio *TL* **1997**, *38*, 7143
TL **1998**, *39*, 2667
Tetrahedron **1999**, *55*, 8189

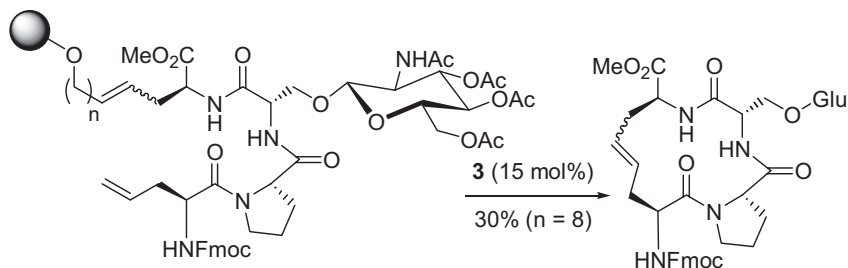
Scheme 2.2-126

Frieboes *TL* **2000**, *41*, 9153

Scheme 2.2-127

Miller *JACS* **1999**, 121, 11638

Scheme 2.2-128

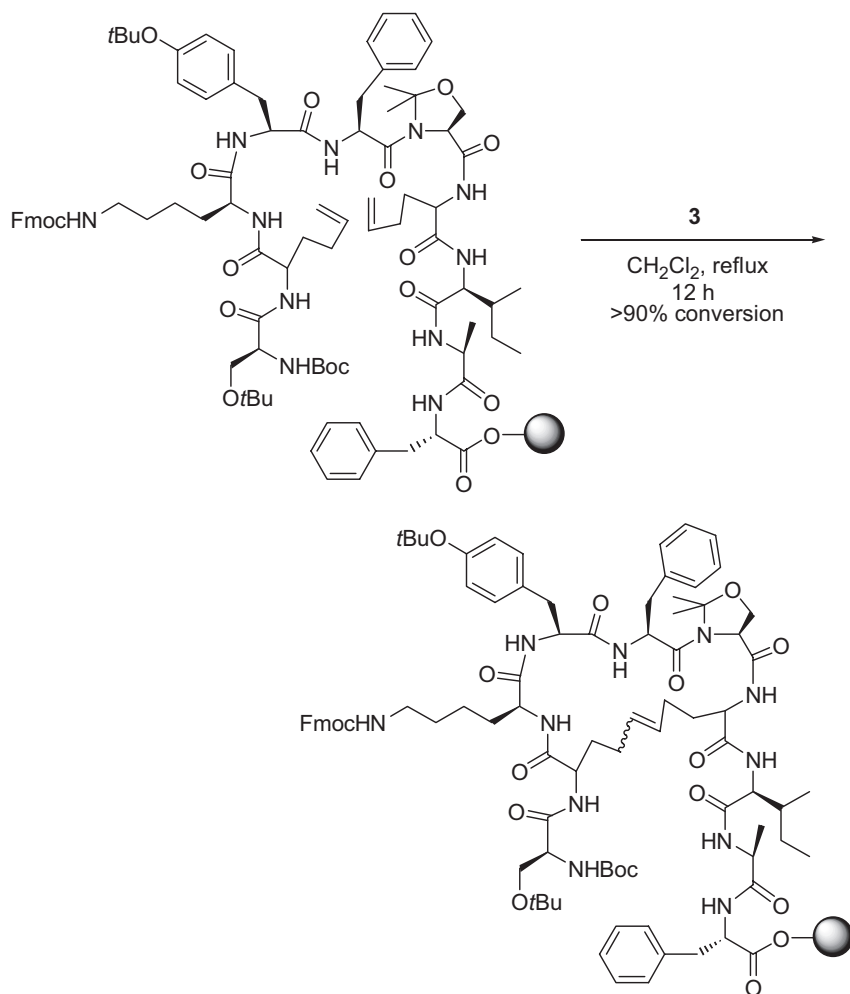
Blechert *CC* **1997**, 1949

Scheme 2.2-129

sites were chosen as ($i + 1$) and ($i + 6$) positions of the acyclic octapeptide β -hairpin precursor. Kinetic evaluation of this cyclized peptide revealed that substituents in the peptide backbone were more important than covalent stabilization of a structural motif for better stereoselectivity.

Catalytic cyclization/cleavage of tetrapeptide-derived macrocycles from solid support (tritylpolystyrene) was studied by Blechert (Scheme 2.2-129) [187]. The solid-supported diolefinic tetrapeptide was smoothly cyclized, depending on the spacer length and mobility of the polymer-supported intermediates. Replacement of proline with alanine or glycine resulted in much slower cyclization rates, demonstrating the importance of β -turn-like structures for the cyclization.

Kessler recently found that reversible backbone protection resulting from introducing a secondary structure-disrupting moiety into a protein-derived homodetic 10-mer peptide epitope could be used to generate a set of cyclic peptides with ring sizes varying from 19 to 27 atoms and different stereochemical orientations at

Kessler *OL* **2002**, 4, 59

Scheme 2.2-130

the bridging positions using RCM methods on solid phase (Scheme 2.2-130) [188]. Terminal butenyl and pentenyl side chains showed high conversion rates (>90%) in RCM reactions, suggesting their appropriateness for the syntheses of small libraries.

2.2.7

Synthesis of Macrocycles

RCM has recently been recognized as one of the most appropriate synthetic methods for the formation of large-ring systems. The major consideration of RCM for

the synthesis of highly flexible large-ring systems is the conformational predisposition of starting material for favorable intramolecular cyclization. It has been well demonstrated that macrocyclization metathesis is highly efficient not only with substrates having suitable restrictions but also with dienes devoid of any rigorous conformational constraints by modification of the reaction conditions such as using highly dilute concentrations. During the RCM, competing reactions such as oligomerization and catalyst decomposition can also proceed, depending on the conformational constrain, concentration, and temperature effects. Higher reaction temperature and lower concentration of the substrate usually favors ring closure and disfavors oligomerization. This reaction condition result in competing catalyst decomposition. Therefore, closure of larger rings generally requires higher catalyst loading compared with smaller rings.

2.2.7.1

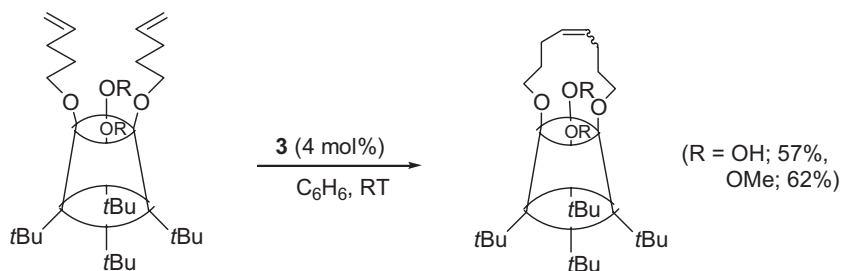
Macrocycles

Bridged calix[4]arene derivatives have been efficiently prepared by RCM (Scheme 2.2-131) [189]. Similar yields of cyclic compounds were obtained for dienes with free hydroxyl groups or in the form of dimethyl ethers.

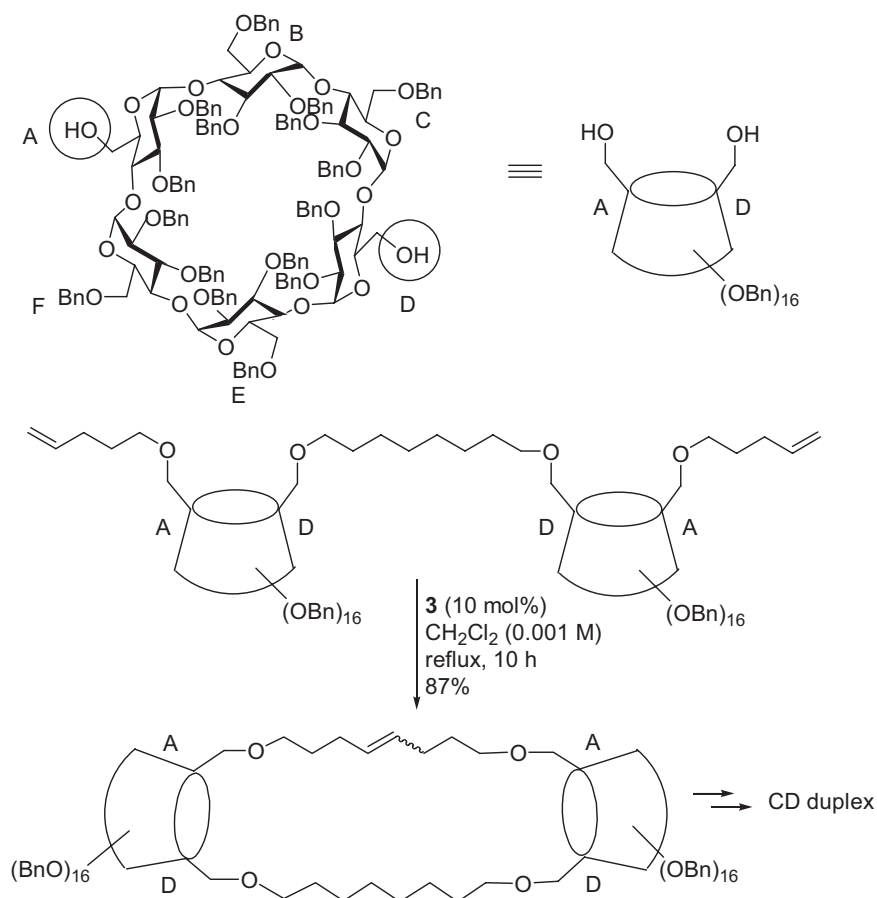
Symmetrical doubly connected head-to-head α -cyclodextrin dimer was also synthesized in high yield using acyclic diene metathesis followed by RCM to afford a novel type of neoglycolipid (Scheme 2.2-132) [190]. The overall yield for the synthesis of CD duplex was 49% from α -CD, whereas previous preparations of doubly linked CDs were in the range of 2–5%.

Core structures of archaeal macrocyclic membrane lipids have been prepared by employing RCM (Scheme 2.2-133) [191]. Reaction of α,ω -diene in the presence of **3** provided the closed 36-membered ring as a major product ($E/Z = 7:1$) under highly dilute concentrations. An increase of the substrate concentration resulted in diminishment of the RCM, and the amounts of the dimerized compound increased significantly.

Luning reported the synthesis of concave 1,10-phenanthrolines by RCM in good yields. Tetraalkene precursors were cyclized by metathesis under thermodynamic



Scheme 2.2-131

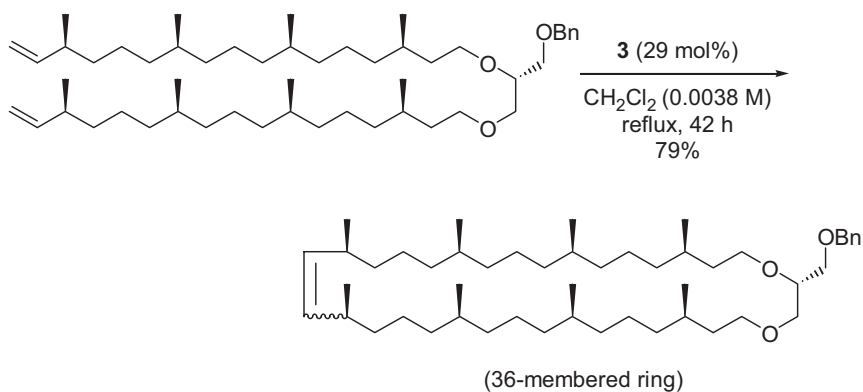
Sinay *TL* **2002**, 43, 5533

Scheme 2.2-132

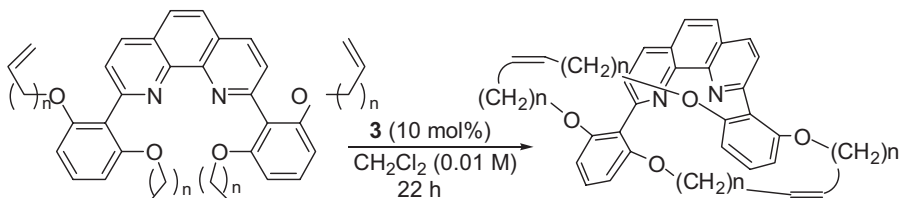
control to give the most stable bimacrocycles, 1,10-phenanthrolines, in yields of up to 92% (Scheme 2.2-134) [192].

Carbohydrate-based spacer-linked macrocycles were also synthesized via RCM as potential binders to polynucleotides (Scheme 2.2-135) [193]. The configuration in the carbohydrate moiety played an important role in RCM process. *Arabino*-configured substrate afforded the intramolecular ring-closed product in good yield, whereas the *ribo*-configured substrate gave the cyclic dimer as the major product and the trimer as a minor product.

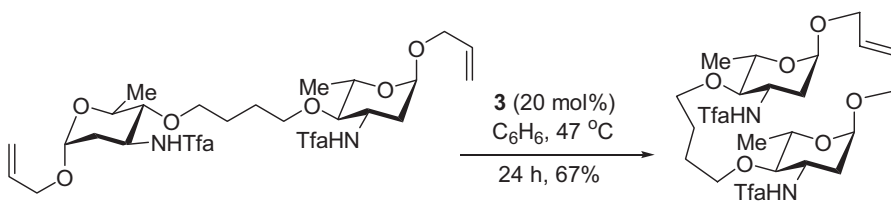
Ibrahim successfully synthesized crown formazans (tetra-azacrown compounds) and crown amides using RCM with catalyst **3** (Scheme 2.2-136) [194, 195]. RCM techniques afforded *cis* double bonds almost exclusively for the crown-formazan derivatives. The azacrown-ether derivatives with 8- to 24-membered ring sizes were also synthesized by the same group in good to excellent yields.

Kakinuma *JOC* **1998**, 63, 4741

Scheme 2.2-133

Luning *EJOC* **2001**, 2161

Scheme 2.2-134

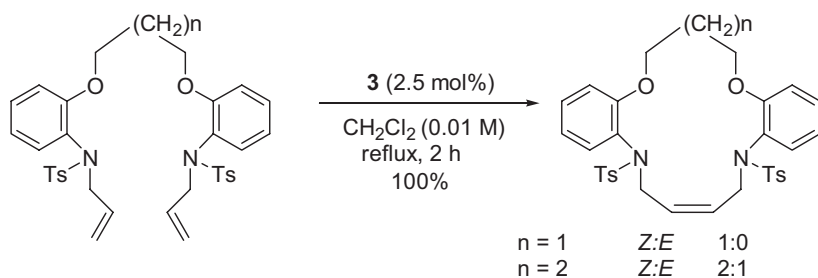
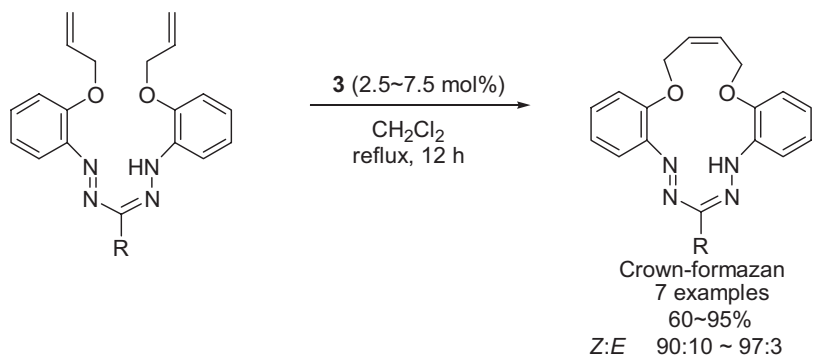
Kirschning *CEJ* **2002**, 8, 2717

Scheme 2.2-135

2.2.7.2

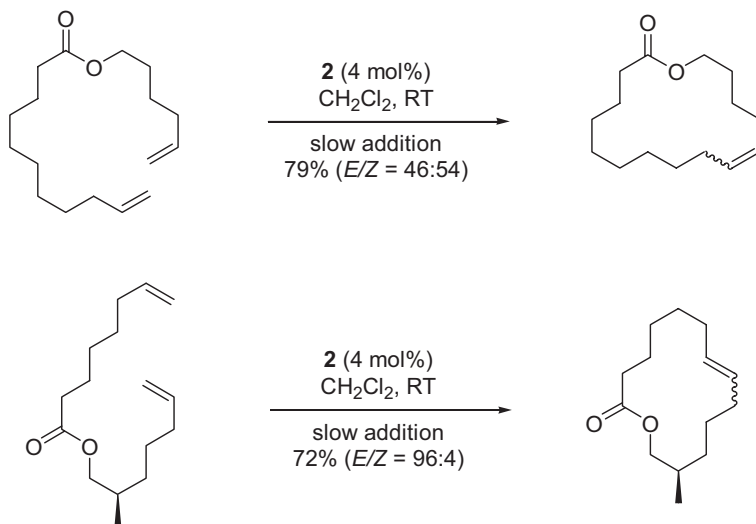
Macrolactones

By introducing structural elements into acyclic precursors, the selectivity of the produced macrocycles by the metathesis reaction is significantly influenced in many cases. Scheme 2.2-137 illustrates macrocyclization of acyclic dienes using RCM. Cyclization of highly flexible α,ω -dienes using slow addition conditions



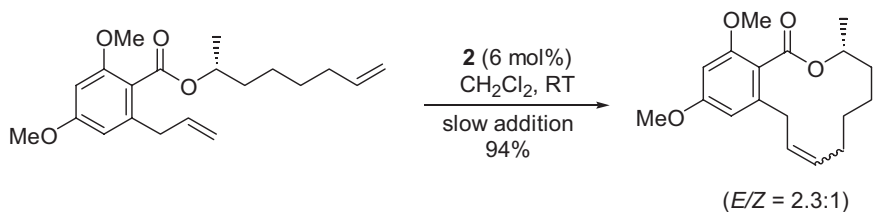
Ibrahim *TL* **2002**, 43, 6971
TL **2002**, 43, 4207

Scheme 2.2-136

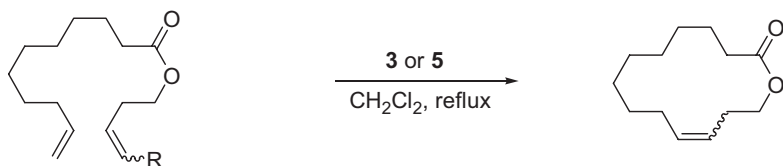


Scheme 2.2-137

Fürstner *JOC* **1996**, 61, 3942

Füstrner *TL* **1996**, 37, 7005

Scheme 2.2-138



R = H: **3** (5 mol%, 5 h), 97%, $E/Z = 4.5:1$
5 (1 mol%, 40 min), >99%, $E/Z = 12:1$

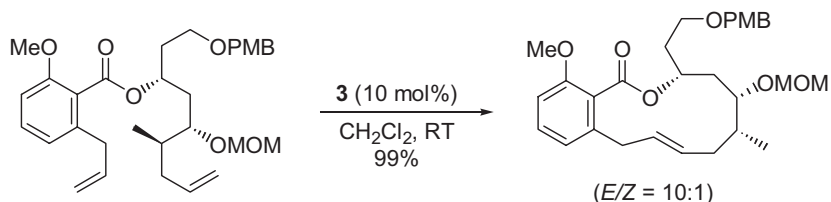
Grubbs *OL* **2000**, 2, 2145

Scheme 2.2-139

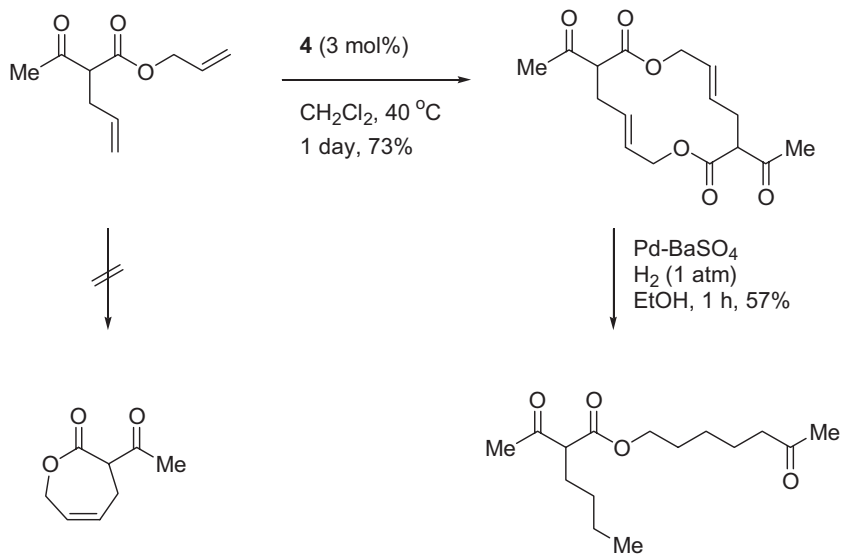
afforded the 16-membered lactone, an olefinic precursor of exaltolide that is a valuable perfumery ingredient [196]. It is surprising that RCM of the substrate containing a remote methyl group to the terminal olefin provided the 14-membered lactone with such high stereoselectivity. This result is in stark contrast to the almost statistical ratio obtained in the cyclization the substrate bearing no substituent at the same position, and suggests that the stereochemistry is kinetically controlled.

A 12-membered bicyclic macrolide has been synthesized via an RCM reaction (Scheme 2.2-138) [197]. Cyclization was cleanly achieved by slowly combining two solutions of the diene and the ruthenium catalyst **2** via dropping funnels. The reaction was essentially quantitative, affording the 12-membered macrocyclic products as a mixture of *E* and *Z* isomers.

Although macrocyclization RCM has been demonstrated to be highly efficient not only with substrates having suitable restrictions but also with dienes devoid of any rigorous conformational constraints, stereoselectivity in the produced macrocyclic alkenes changes with ring sizes and substituents of the substrates. Therefore, control of selectivity in macrocyclization is one issue that still has to be addressed in order to make this RCM more predictable. From this aspect, an interesting result has appeared in the literature in the macro-RCM studies using the more recently developed ruthenium complex **5** (Scheme 2.2-139) [198]. The final *E/Z* ratio of the 14-membered lactone was dependent on the catalysts employed

Brabander *ACIEE* **2000**, 39, 4308

Scheme 2.2-140

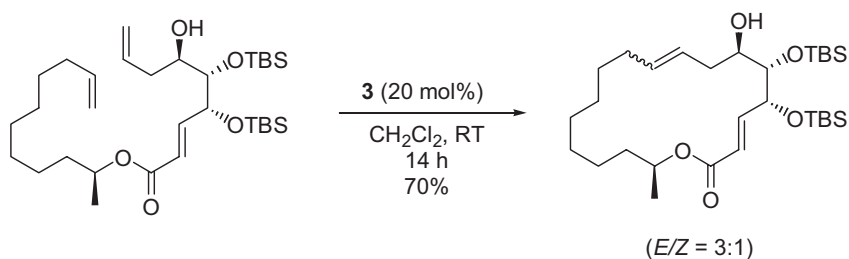
Christoffers *Synlett* **2002**, 957

Scheme 2.2-141

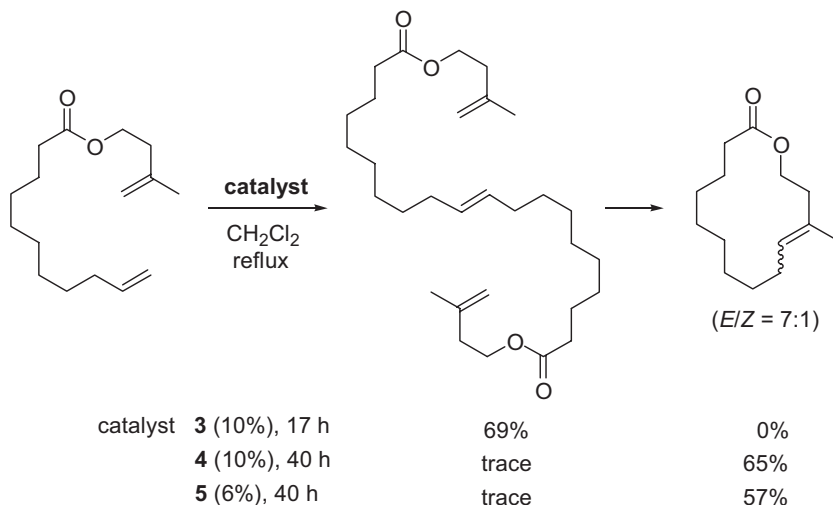
regardless of the presence of auxiliaries or initial alkene stereochemistry, in which more active catalyst **5** gave significantly higher *trans* selectivity than did **3**. It turned out that the higher E/Z with complex **5** mainly originated from secondary metathesis reactions that isomerize the initially lower E/Z ratio to the higher thermodynamic value.

A recent total synthesis of salicylihalamides, a family of natural products of antitumor activity, illustrates another utility of RCM for the formation of macrocycles [199–201]. The RCM reaction of diolefinic ester with ruthenium catalyst **3** gave the cyclized 12-membered lactonide in excellent yield with the preference for the *E* isomer (Scheme 2.2-140).

When a diallyl β -ketoester was subjected to RCM reaction in the presence of Ru catalyst **4** without $\text{Ti}(\text{Oi-Pr})_4$, a 14-membered bislactone was formed instead of a 7-membered lactone (Scheme 2.2-141) [202]. Although macrocyclization by RCM

Banwell OL **2000**, 2, 3583

Scheme 2.2-142

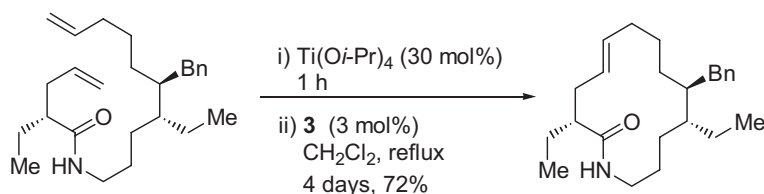
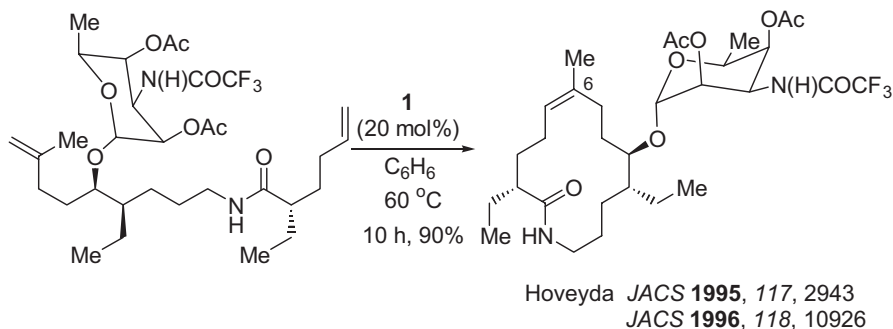
Fürstner OL **2001**, 3, 449

Scheme 2.2-143

is generally known to be non-stereoselective in C–C double bond configuration, more than 95% of the *E,E*-configured bislactone is obtained, presumably due to the reversibility of the RCM reaction with a strain or steric hindrance in the *Z* isomer.

An example of a cyclization/reduction strategy for the formation of macrocycles was revealed by Banwell [203]. (+)-Aspicilin served as a target compound, and the 18-membered lactone ring of the natural product was prepared by the RCM of dialkenyl ester (Scheme 2.2-142). The ruthenium carbene **3**-catalyzed RCM of the substrate proceeded smoothly to give the lactone in moderate yield with slight preference for the *E* isomer.

A trisubstituted alkene-containing macrolactone was synthesized from the corresponding diene using RCM. The macrocyclization of the diene proceeded via the dimeric acyclic intermediate with the newer generation of ruthenium catalysts, indicating the ready reversibility of olefin metathesis (Scheme 2.2-143) [204]. After



Bracher *Synlett* **2002**, 1724

Scheme 2.2-144

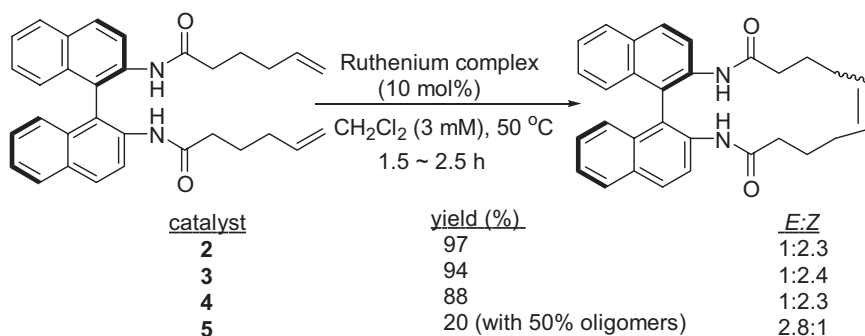
a 4-h reaction time with catalyst **4** or **5**, the acyclic intermediate was formed as the major product along with the desired 14-membered lactone in small amounts. However, when the reaction was heated for 40 h, the intermediate almost disappeared, while the desired cyclic lactone was formed as the major product. With the less reactive catalyst **3**, on the other hand, a smooth dimerization at the least substituted site occurred, but a subsequent cyclization to form the desired cyclic product did not proceed upon prolonged reaction time.

2.2.7.3

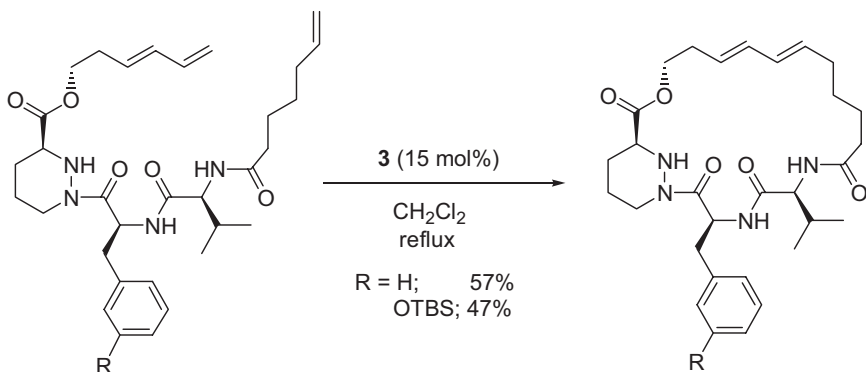
Macrolactams

Hoveyda synthesized a macrolactam antifungal agent, Sch 38516 (fluvirucin B₁), based on an RCM reaction (Scheme 2.2-144) [205, 206]. The trisubstituted diolefin bearing a carbohydrate pendant was effectively cyclized into a macrolactam in excellent yield by the action of the molybdenum catalyst **1**. Stereocontrolled hydrogenation of the olefin and removal of the protecting groups delivered the target compound. Bracher later utilized ruthenium catalyst **3**, which is easier to handle than **1**, in RCM for the synthesis of an aglycone 6-nor-fluvirucin B₁ [207].

Nakagawa examined the stereoselectivity in RCM of tethered dihexenoyl derivatives under various conditions. The *E*:*Z* ratios of the resulting double bonds of the cyclic bislactam were examined, and it was found that the stereochemical outcome in RCM was largely dependent upon the substrate structures (Scheme 2.2-145) [208, 209].

Nakagawa *JCSPT1* **2002**, 959

Scheme 2.2-145

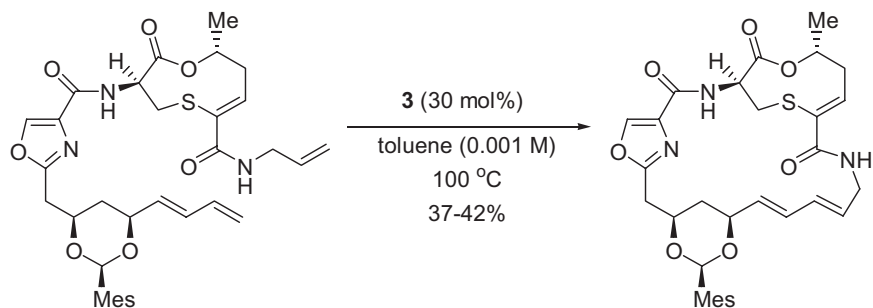
Wagner *ACIEE* **1999**, 38, 2443
JOC **2000**, 65, 9255

Scheme 2.2-146

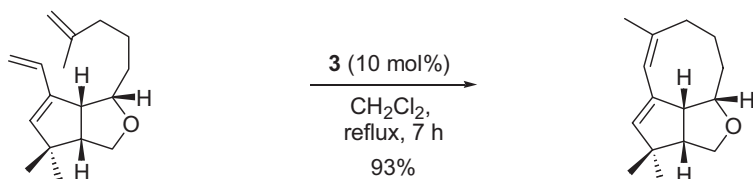
2.2.8

Synthesis of Cyclic Conjugated Dienes

Wagner disclosed the first example of the construction of a macrocyclic conjugated 1,3-diene by the direct RCM reaction in a sequence directed toward the synthesis of synthetic analogues of sanglifehrin A (SFA), which binds to cyclophilin, an intracellular binding protein (Scheme 2.2-146) [210, 211]. The macrolide contains a tripeptide unit composed of piperazic acid, *meta*-tyrosine, and valine. Interestingly, the peptide backbone extends through the β -nitrogen atom of piperazic acid rather than its α -nitrogen atom. The ring-closure reaction was best performed under highly dilute concentrations (<5 mM) in CH_2Cl_2 under reflux with ruthenium-carbene complex **3** (15 mol%) to afford the 22-membered conjugated diene product. This example of conjugate cyclic diene synthesis should be of high interest for organic synthesis in general, natural product synthesis, and medicinal chemistry in particular.

Meyers *ACIEE* **2000**, 39, 1664

Scheme 2.2-147

Paquette *JACS* **2000**, 122, 2742

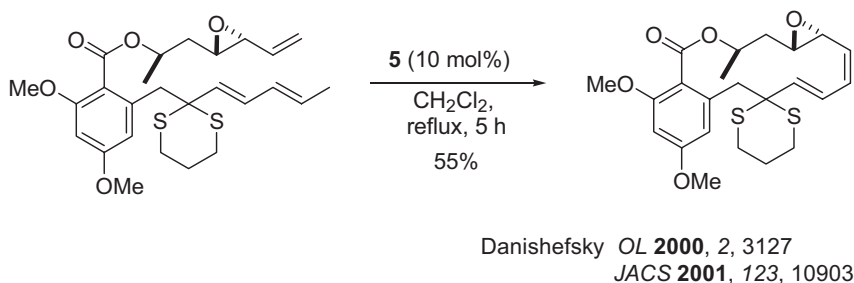
Scheme 2.2-148

Using the RCM strategy for the formation of conjugated cyclic dienes, Meyers reported the first successful synthesis of (–)-griseoviridin as well as its C-8 epimer (Scheme 2.2-147) [212]. The ring-closing metathesis of the conjugated diene substrate using **3** (30 mol%) furnished the 23-membered conjugated diene product in 37–42% yield. No isomerization of the double bond in the product was observed during the RCM.

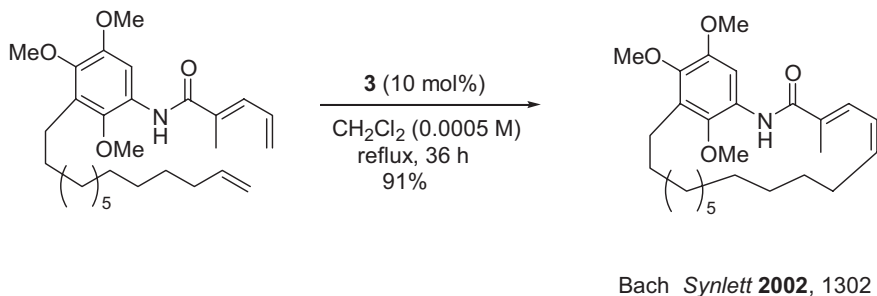
Paquette also used the RCM strategy of conjugated diolefinic substrate for the synthesis of (+)-asteriscanolide (Scheme 2.2-148) [213]. In this approach, the conjugated 8-membered ring was produced with the action of **3** in a remarkably high yield, considering the factors impeding the formation of 8-membered rings in general. The limited conformational flexibility of the side chain in the substrate was claimed to serve to facilitate the ring closure.

The extremely appealing utility of RCM has been recently exemplified by Danishefsky for the synthesis of a 14-membered macrolide, radicicol [214, 215]. RCM of the highly functionalized substrate having a diolefinic vinyl epoxide was successfully carried out using the recently developed catalyst **5** to afford the desired lactone in 55% yield (Scheme 2.2-149). In contrast, only trace amounts of the product were obtained with **3**.

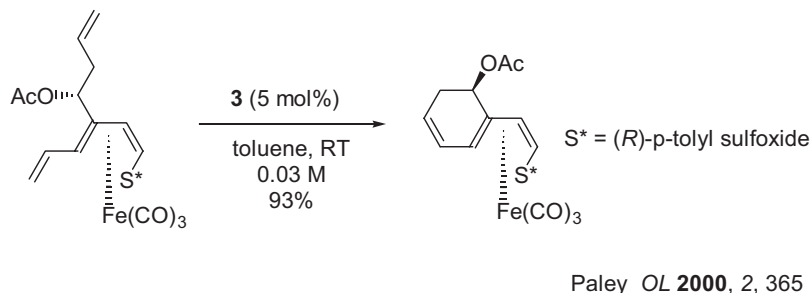
Bach disclosed the synthesis of *ansa*-bridged conjugated lactams related to the antitumor antibiotic geldanamycin by RCM (Scheme 2.2-150) [216]. The *Z* isomer



Scheme 2.2-149



Scheme 2.2-150

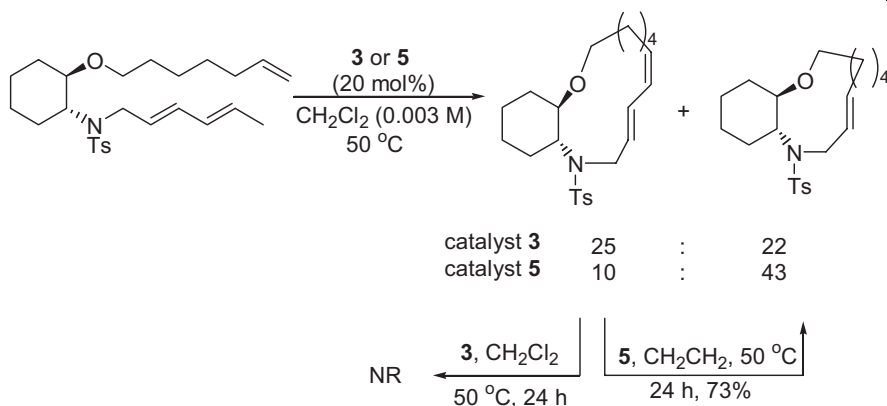


Scheme 2.2-151

was exclusively formed during the RCM reaction. The macrocyclization proceeded cleanly and in good yield under high dilution conditions.

RCM of an iron-complexed conjugated trialkenyl substrate was successfully carried out with **3** to give a conjugated carbocycle in excellent yield (Scheme 2.2-151) [217]. It is notable that the ruthenium catalyst was compatible with the sulfoxide as well as the iron tricarbonyl unit.

Paquette systematically analyzed the intramolecular competition associated with the RCM of ene-diene systems of differing chain lengths [218]. Chemical evolution of cyclic (*Z*)- and (*E*)-monoenes as well as cyclic conjugated (*E,Z*)- and (*E,E*)-dienes by RCM of the corresponding ene-diene is considered to be dependent of prevailing kinetic and thermodynamic factors. When the conjugated (*E,Z*)-diene RCM

Paquette *HCA* 2002, 85, 3033

Scheme 2.2-152

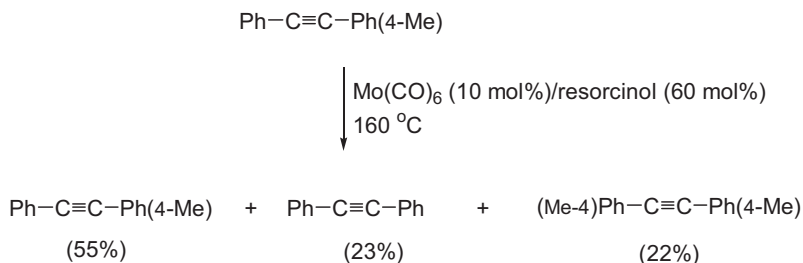
product was re-subjected to the original RCM conditions, only the more reactive ruthenium catalyst 5 furnished the ring-contracted (*E*)-monoene in good yield, suggesting that the conversion of the triene precursor to the cyclic monoene may proceed via the intermediacy of the cyclic conjugated diene (Scheme 2.2-152).

2.2.9

Alkyne Metathesis

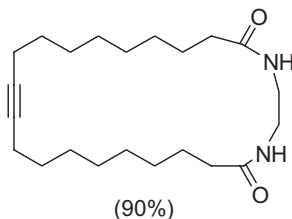
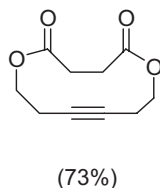
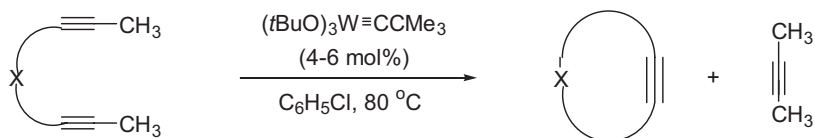
Although RCM of dienes has recently been firmly established as a remarkable tool for the organic community, sometimes more predictable control over the configuration of the newly formed double bond is necessary for the formation of macrocyclic compounds in particular. For completeness, a few examples of the use of alkynes in olefin metathesis will be included here. More complete discussions are in other chapters of this handbook (Chapter 2.12). As an indirect approach to attain required olefin geometry, ring-closing alkyne metathesis followed by partial reduction of the resulting cycloalkynes would be a viable alternative provided that preparation of the dialkynyl substrates is practical and that metathesis efficiency of the alkynes is comparable to that of the dienes. Mortreux reported the first example of alkyne metathesis with a $[\text{Mo}(\text{CO})_6]/\text{resorcinol}$ catalyst generated *in situ* (Scheme 2.2-153) [219, 220]. Attempts to convert terminal alkynes were unsuccessful with this catalyst system. Mortreux also showed that the metathesis of dialkynes could be carried out photochemically at room temperature with catalyst systems that are generated *in situ* if both *meta*-chlorophenol and $[\text{Mo}(\text{CO})_6]$ are present in the reaction solution [221].

Despite the potential utility of the alkyne metathesis, this area has remained in the shadow of alkene metathesis primarily due to harsh reaction conditions and limited functional group tolerance of the catalyst systems [222]. As a result, appli-



Mortreux *CC* **1974**, 786
JMC **1977**, 2, 73
JMC **1982**, 15, 93

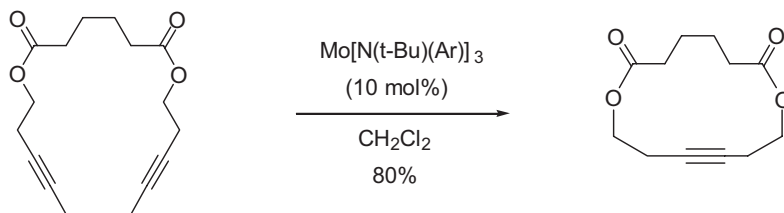
Scheme 2.2-153



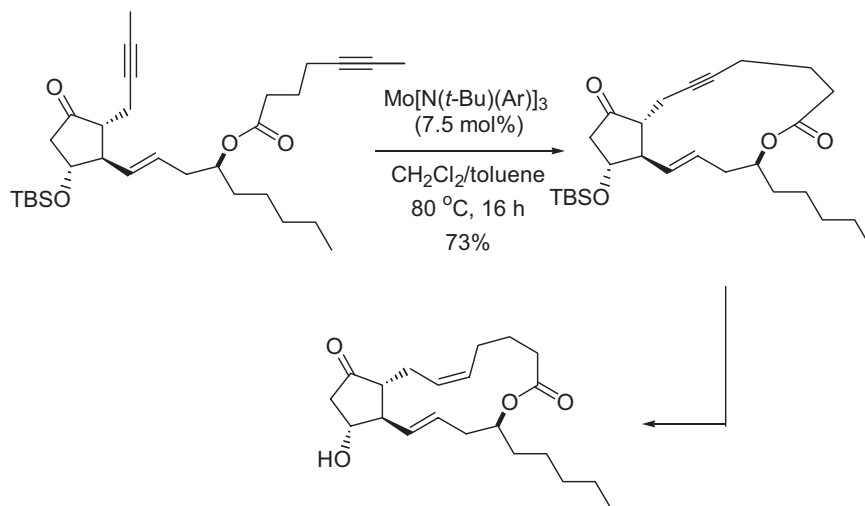
Fürstner *ACIEE* **1998**, 37, 1734

Scheme 2.2-154

cations of the alkyne metathesis have been confined to the preparation of some special polymers [223–225] and to the dimerization or cross-metathesis of simple acetylene derivatives [226, 227]. Fürstner disclosed the first application of alkyne metathesis for the formation of macrocyclic alkynes using Schrock's tungsten-alkylidyne complex $[(\text{tBuO})_3\text{W}\equiv\text{CCMe}_3]$ as the catalyst (Scheme 2.2-154) [228]. Because various functional groups unexpectedly tolerated the W-carbyne complex, it was possible to obtain lactones, lactams, and cyclic silyl ethers of ring sizes 12 or larger in good yields. Various solvents such as trichlorobenzene, chlorobenzene, toluene, or THF could be employed without greatly affecting the yields. It is significantly notable that the catalyst rigorously distinguishes between alkynes and olefinic groups in the substrates, which were found to be inert. However, internal

Fürstner *JACS* **1999**, 121, 9453

Scheme 2.2-155

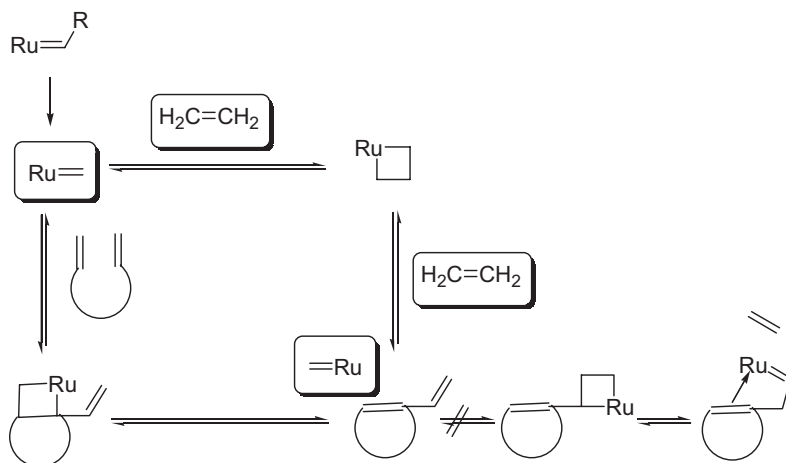
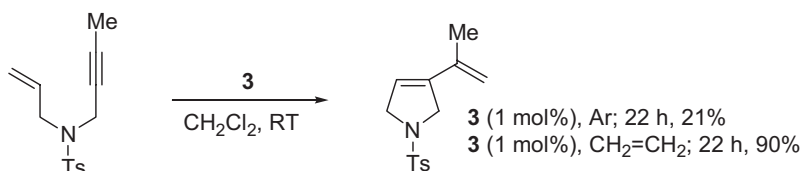
Fürstner *ACIEE* **2000**, 39, 1234

Scheme 2.2-156

alkynes have to be used as substrates because terminal alkynes are compatible with the catalyst system.

Tris-amido molybdenum complexes of the general type $\text{Mo}[\text{N}(\text{t-Bu})(\text{Ar})]_3$ have been also utilized as reactive metathesis catalysts of alkynes in combination with halide sources such as CH_2Cl_2 or TMSCl [229–231]. It is believed that the halide sources activate the Mo complexes to form the corresponding halide complexes, and thus the formed tris-amido molybdenum(IV) chloride is a catalytically relevant species. The activity of this catalytic system has turned out to be superior in most cases compared to $[(\text{tBuO})_3\text{W}\equiv\text{CCMe}_3]$ or the $[\text{Mo}(\text{CO})_6]/\text{resorcinol}$ system (Scheme 2.2-155).

With these tools in hand, several applications of alkyne metathesis to the total synthesis of bioactive compounds have been reported [230, 232, 233]. Among those, the most notable example is the total synthesis of prostaglandin E2-1,15-lactone (Scheme 2.2-156) [234]. The alkyne metathesis was carried out efficiently



Mori *JACS* **1997**, 119, 12388
JOC **1998**, 63, 6082

Scheme 2.2-157

in the presence of the $\text{Mo}[\text{N}(t\text{-Bu})(\text{Ar})]_3/\text{CH}_2\text{Cl}_2$ system followed by Lindlar reduction of the resulting cycloalkyne to afford the stereochemically determined alkene product.

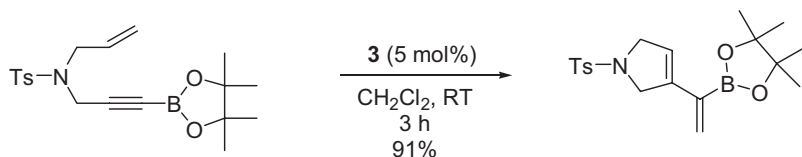
2.2.10

Enyne Metathesis

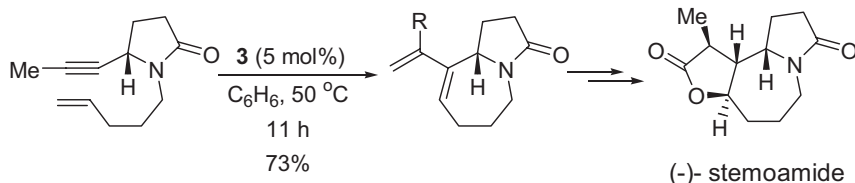
2.2.10.1

General Enyne Metathesis

A metathesis reaction using a metal-carbene complex has become an essential tool for organic synthesis (Chapter 2.5). RCM of enynes is quite an interesting reaction because double bonds and triple bonds are cleaved and multiple bonds are formed at the same time. Mori found that ethylene has profound effects on the rates and efficiency of enyne metathesis [235, 236]. While reaction of enynes with the ruthenium carbenes proceeds slowly under inert gas atmosphere, the reaction rate of the same reaction is much faster under the ethylene gas, providing diene product with higher yields (Scheme 2.2-157). The presence of ethylene gas helps to main-

Renaud *ACIEE* **2000**, 39, 3101

Scheme 2.2-158

Mori *JOC* **1996**, *61*, 8356

Scheme 2.2-159

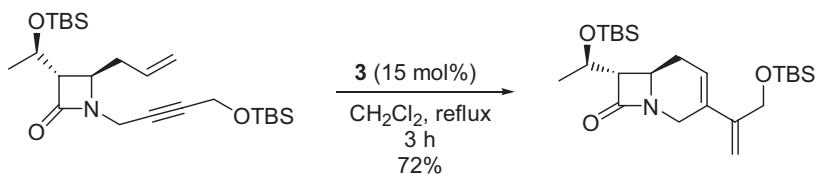
tain the concentration of the active catalytic species, methylidene-ruthenium complex, higher than in the absence of the gas by inhibiting the reaction of the active species with the diene product.

In connection with the RCM of dienes having boronates, Renaud expanded the substrate scope of enyne metathesis reactions [237]. RCM of en-1-ynylboronic esters in the presence of **3** (5–10 mol%) furnished the 5-, 6-, and 7-membered carbocyclic and heterocyclic 1,3-dialkenyl-2-boronates in good to excellent yields (Scheme 2.2-158). The produced 1,3-dialkenyl compounds underwent further transformation such as Diels-Alder reactions to give vinyl boronates of higher molecular complexity in a short sequence of steps.

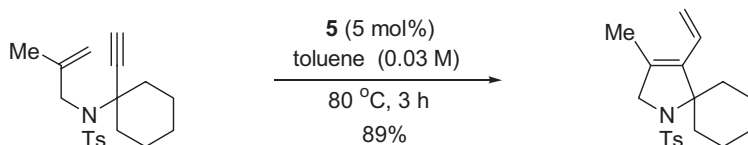
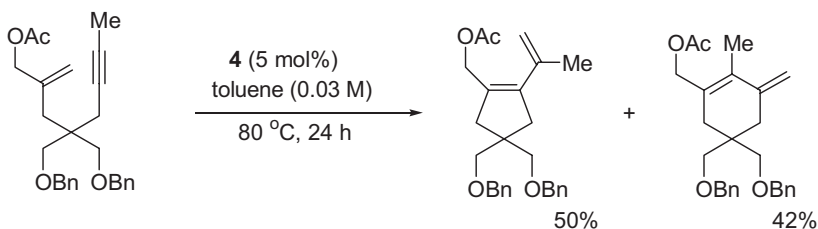
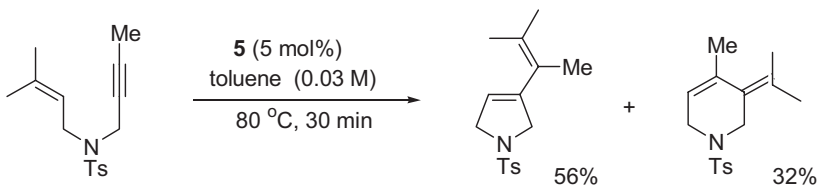
Intramolecular enyne metathesis has been applied in the total synthesis of a natural product, (–)-stemoamide from (–)-pyrroglutamic acid (Scheme 2.2-159) [238]. Enyne substrates were converted into the corresponding 5,7-fused ring system by the action of ruthenium catalyst **3**, with the efficiency depending on the types of substituents of the terminal alkyne. Surprisingly, the RCM reaction of enyne having carbomethoxy groups on the alkyne proceeded in respectable yield at room temperature.

Barrett reported a novel method of synthesizing bicyclic β -lactams using enyne RCM [155]. Reaction of monocyclic β -lactams bearing enynes with **3** afforded bicyclic β -lactams in good yields (Scheme 2.2-160). In this reaction, terminal alkyne did not give a good result.

Mori recently examined the effects of substituents of enynes in RCM [239]. Even though catalyst **3** effected enyne metathesis smoothly with a monosubstituted alkene substrate, it did not undergo RCM reaction with an enyne having a disubstituted alkene and an internal alkyne. Instead, the new generation of

Barrett *JOC* **1998**, 63, 7893

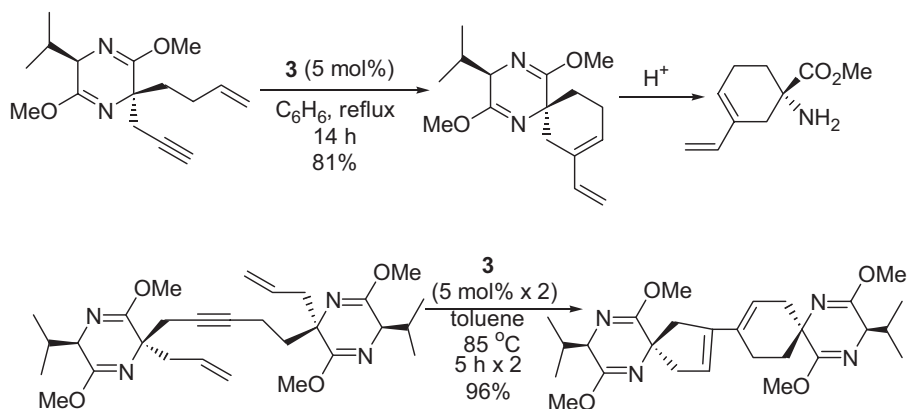
Scheme 2.2-160

1,1-disubstituted alkene and terminal alkyne*1,1-disubstituted alkene and internal alkyne**trisubstituted alkene and internal alkyne*Mori *ASC* **2002**, 344, 678

Scheme 2.2-161

ruthenium-carbene complexes (4 or 5) effected enyne metathesis effectively and in high yield (Scheme 2.2-161).

Undheim described the stereoselective synthesis of cyclic 1-amino-1-carboxylic acids using Ru-catalyzed enyne metathesis [240]. With the treatment with 3 of the



Undheim *Tetrahedron* **1997**, 53, 10603
JCSPT1 **2001**, 2697

Scheme 2.2-162

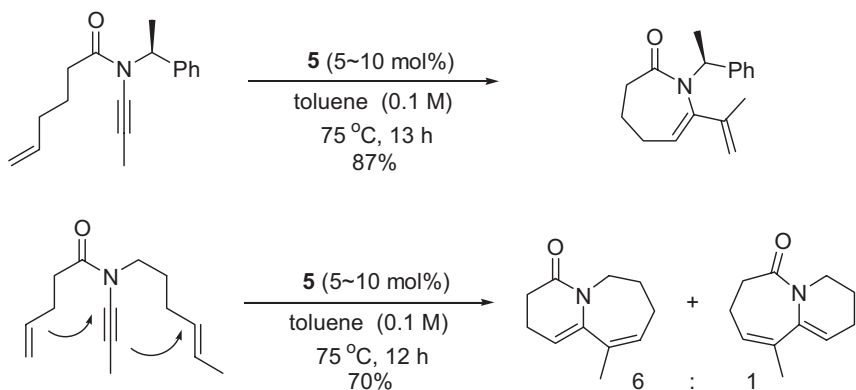
enyne substrates were converted into spiro compounds, which were cleaved to the desired amino acid methyl esters under mildly acidic conditions (Scheme 2.2-162). The same methodology was expanded for the preparation of rigid and annulated tricyclic bis(α -amino acid) derivatives by Ru(II)-catalyzed cased and Diels-Alder reactions [241]. The dienyne substrate underwent RCM reaction almost quantitatively with catalyst **3**. The catalyst was added in two portions due to the low thermal stability of the catalyst during RCM at an elevated reaction temperature [242].

Hsung successfully synthesized cyclic 2-amido-1,3-dienes from enynamides using RCM with catalyst **5** [243]. The dienamide products were further subjected to Diels-Alder cycloaddition conditions to demonstrate their synthetic utility. The enynamide substrate was readily prepared from the corresponding propargyl amine via an *N*-acylation followed by a base-induced isomerization of the resulting propargyl amide to the chiral enynamide. The choice of the solvent and the reaction temperature was critical in the efficiency of the metathesis reaction. The first tandem RCM of dienynamides with two sterically differentiated alkenyl substituents was also reported (Scheme 2.2-163).

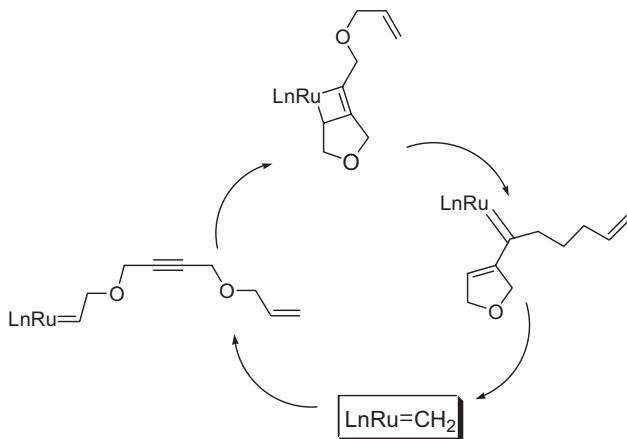
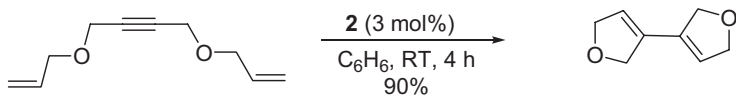
2.2.10.2

Dienyne Metathesis

Enynes, in addition to dienes, are considered a good metathesis substrate class. The formation of a fused bicyclic [*n,m,0*] ring system was observed via Ru-carbene-catalyzed double RCM of acyclic dienynes, in which the triple bond positioned between the two olefins acts as an olefin metathesis relay (Scheme 2.2-164) [244, 245]. This strategy provides functionalized fused bicyclic compounds containing 5-, 6-, and 7-membered rings in a highly selective manner. The acetylenic substituents

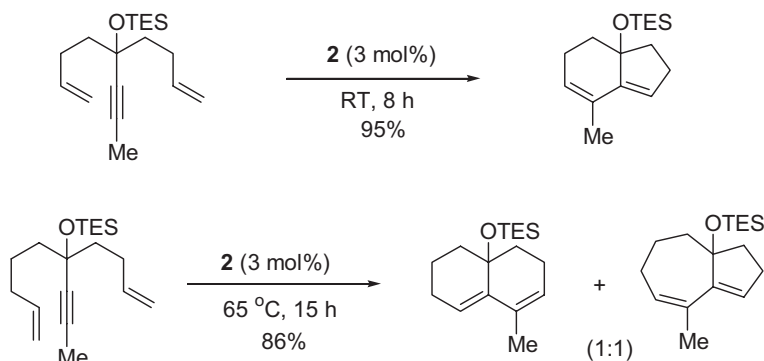
Hsung *OL* **2002**, *4*, 2417

Scheme 2.2-163

Grubbs *JACS* **1994**, *116*, 10801
JOC **1996**, *61*, 1073

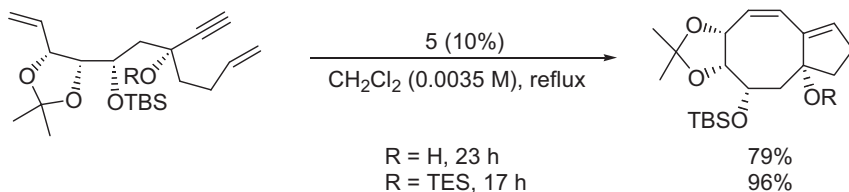
Scheme 2.2-164

in the substrates are transferred into vinylic pendants of the cyclized products, which could be subsequently manipulated into more diverse functionalities. It is also noteworthy that no atom is lost during the enyne metathesis as compared to diene metathesis, in which a volatile terminal alkene such as ethylene is re-



Grubbs *JACS* **1994**, *116*, 10801
JOC **1996**, *61*, 1073

Scheme 2.2-165



Hanna *OL* **2001**, *3*, 3095

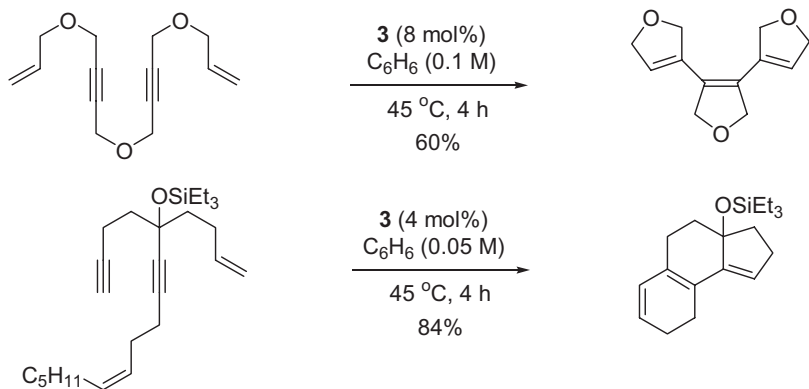
Scheme 2.2-166

pelled from the substrates. It is presumed to proceed by the first reaction of terminal olefin of the diene with carbene complex to produce a new Ru carbene, which in turn cycloadds into internal alkyne, affording metallacyclobutene. Retro-cycloaddition and subsequent ring closure end with the bicyclic product.

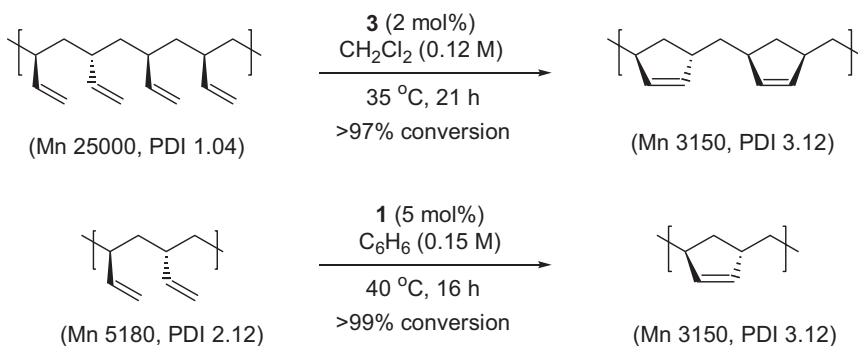
Bridged and fused bicyclic systems containing medium-sized rings exist in biologically important natural products. Fused bicyclic ring systems can be obtained using an RCM reaction by placing the alkynyl group as a chain in substrates (Scheme 2.2-165) [246]. While symmetrical diene-yne is converted into a fused bicyclic ring system as a single product, reaction of an unsymmetrical substrate gives two different bicyclic ring systems with the same ratio.

With catalyst 5, polyoxygenated bicyclic systems containing medium-sized rings from carbohydrates were synthesized from corresponding diene-yne by RCM. Thus, highly functionalized carbobicyclic systems containing 7- and 8-membered rings were constructed in good yields (Scheme 2.2-166) [247].

In principle, the tandem enyne metathesis reactions can be extended to “multi-cyclization” by attaching additional metathesis relays such as acetylenic or olefinic groups. This concept was realized by Grubbs, and one-step tricyclization was

Grubbs *JOC* **1998**, 63, 4291

Scheme 2.2-167

Grubbs *JACS* **1996**, 118, 229

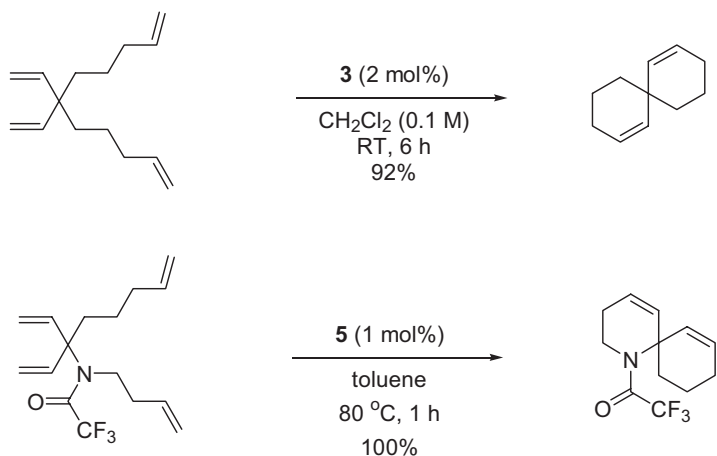
Scheme 2.2-168

accomplished by the metathesis of dienediynes (Scheme 2.2-167) [246]. Depending on the dienyndiynes utilized, either non-fused or fused tricyclic triene systems were produced in the presence of ruthenium catalyst **3**.

2.2.11

Multi-Directional RCM

RCM of simple α,ω -dienes has been extended to polymeric substrates containing suitably spaced olefins (Scheme 2.2-168) [248]. Atactic 1,2-polybutadiene was treated with Ru carbene **3** to afford the cyclopolymer product cleanly. The lower molecular weight (M_n) and broader polydispersity (PDI) of the polycyclopentene



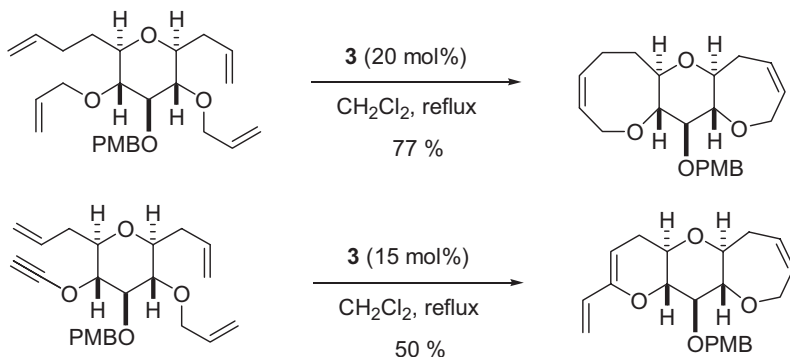
Harrity *TL* **1999**, 40, 3247
CC **2002**, 1542

Scheme 2.2-169

compared to the starting material suggest that metathetical degradation of the infrequent 1,4-divinyl units of the polymer backbone occurs during the RCM process. The reaction proceeded to 90% conversion in the first 30 min and then continued slowly to 97% conversion in the next 3 h. Reaction of syndiotactic 1,2-poly(*Z*-pentadiene) with molybdenum catalyst **1** yielded the *trans*-diisotactic cyclo-polymer in quantitative yield. As a dramatic illustration of the reversibility of metathesis reaction, the kinetic profiles suggest that the catalyst randomly closes adjacent olefins until only isolated olefins remain and then migrates up and down the chain until all olefins are cyclized.

Harrity explored the synthesis of spirocycles through the employment of tandem ring-closing metathesis reactions on tetraalkenes [249]. Selectivity for the formation of 5- and 6-membered rings over other ring sizes was significantly high (Scheme 2.2-169). This method can afford a range of functionalized spirocyclic systems with high efficiency. The same methodology was applied to the synthesis of spiropiperidines for the purpose of further nitrogen-directed regio- and stereo-selective functionalization through nitrogen-directed epoxidation [250].

An elegant example of two-directional RCM has been described recently by Clark during the synthetic studies towards ciguatoxin (Scheme 2.2-170) [251]. The RCM reaction of the monocyclic tetraene proceeded with high efficiency to furnish the desired tricyclic ring system. This example is especially good because it is possible to build multicyclic ring systems from a single ring in a two-directional manner.

Clark *ACIEE* **2000**, 39, 372

Scheme 2.2-170

2.2.12

Tandem Processes

2.2.12.1

Tandem ROM/RCM

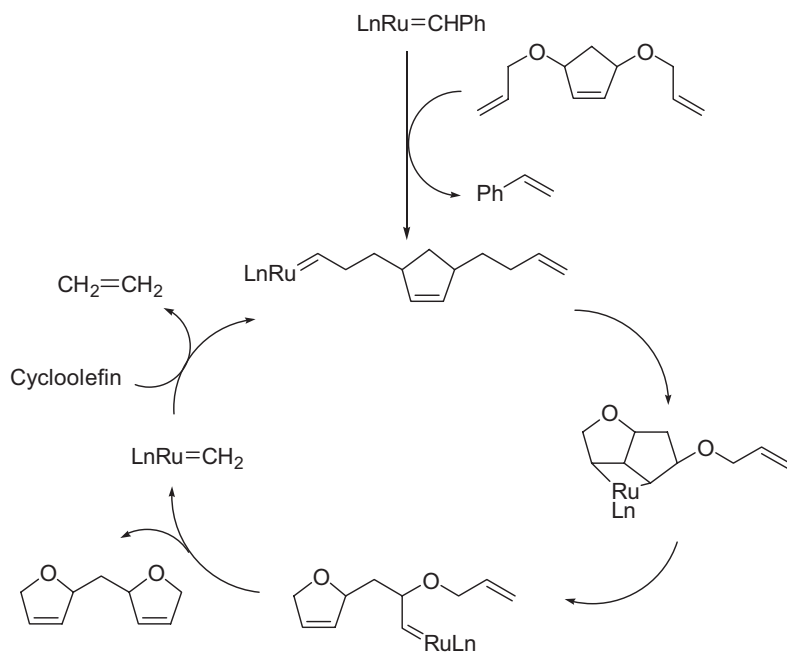
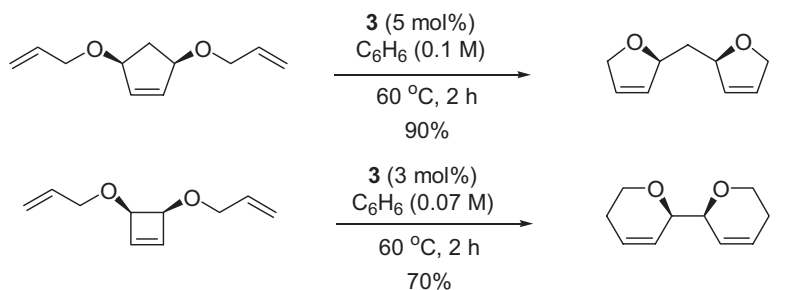
A new strategy for the formation of bicyclic ring systems has been developed in Grubbs' laboratory, in which a tandem intramolecular ring-opening metathesis (ROM) and ring-closing metathesis (RCM) of cyclic olefins (usually 4- or 5-membered rings) containing two alkenyl side chains are performed (Scheme 2.2-171) [246, 252]. This family of reactions allows the rapid synthesis of complex molecules from readily available substrates (see Chapter 2.4).

Hoveyda described RCM-mediated rearrangement of styrenyl ethers to yield heterocyclic products [253–255]. Surprisingly, the yields of the rearranged products were significantly increased under an ethylene atmosphere, as dimer formation was minimized. Chromenes with different lengths of side chain and with various substituents were prepared in good to excellent yields from the reaction of styrenyl ethers with Ru-carbene catalyst **2** (Scheme 2.2-172).

Cyclic α -amino acid esters are also synthesized via ruthenium-catalyzed tandem ROM/RCM, where the 6-membered amino ester cycle formation is the driving force for the reaction (Scheme 2.2-173) [256, 257].

Ruthenium-catalyzed ROM/RCM in a domino process permitted rapid access to a variety of highly functionalized aza- and oxacycles, starting from readily available cyclopentenyl or cycloheptenyl ethers and amines. The chirality embedded in the carbocyclic starting material was completely transferred into the product side chain (Scheme 2.2-174) [258].

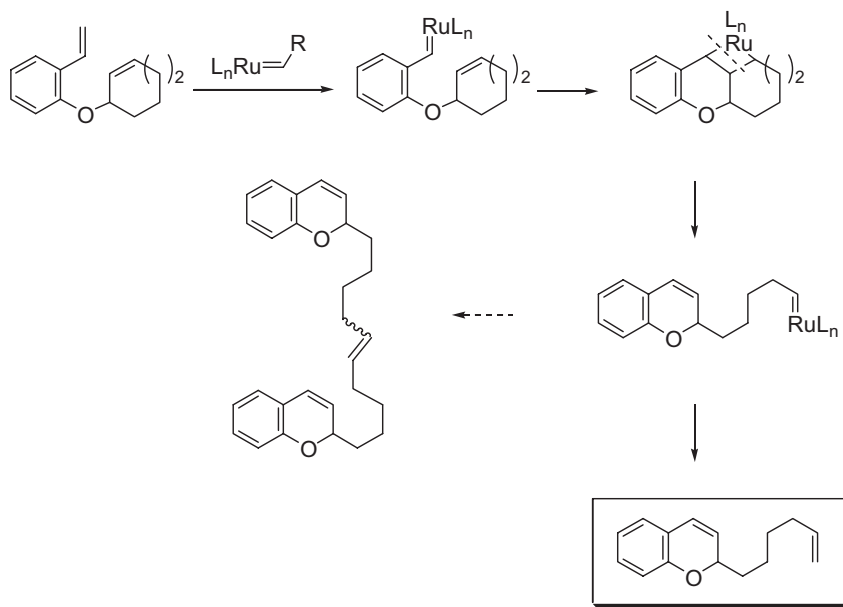
This tandem ROM/RCM approach enabled a new enantioselective synthesis of the indolizidine alkaloid (–)-swainsonine (Scheme 2.2-175) [259]. The sterically

Grubbs *JACS* **1996**, *118*, 6634

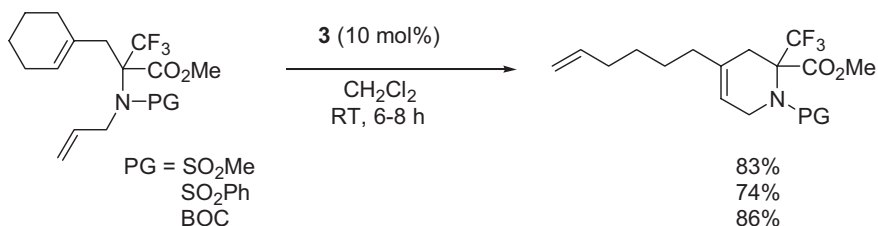
Scheme 2.2-171

demanding TBDMS ether was essential to shift the tandem ROM/RCM equilibrium toward the product, proving that the TBDMS group sterically interacted with the substituent and thus facilitated ring opening while suppressing dimerization of the products. Addition of excess ethylene in the metathesis was also responsible for extremely clean reaction [260].

With the more active catalyst **5**, tandem ROM/RCM as well as tandem enyne RCM/RCM afforded synthetically useful α,β -unsaturated lactones and enones in moderate to excellent yields (Scheme 2.2-176) [261].

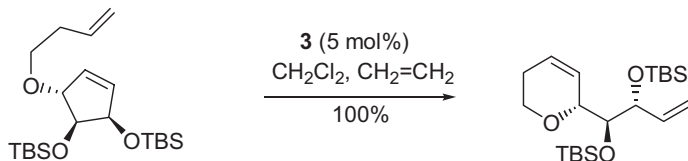
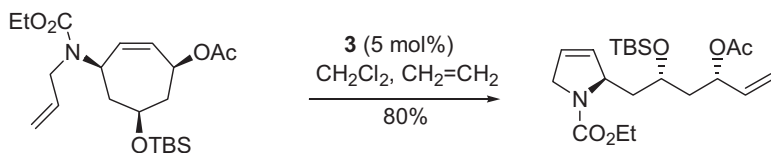
Hoveyda *JACS* **1997**, *119*, 1488

Scheme 2.2-172

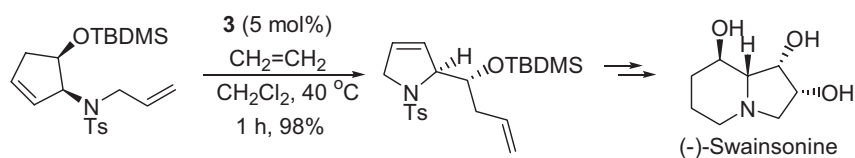
Osipov *Synlett* **2001**, 621
EJOC **2001**, 3891

Scheme 2.2-173

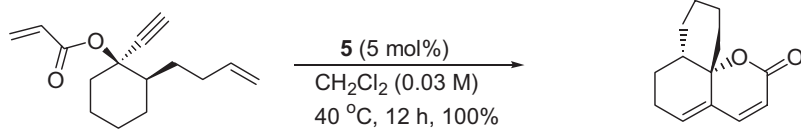
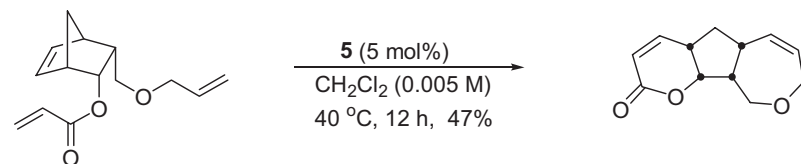
Phillips investigated the tandem ROM/RCM of bicycle[2.2.2]octenes to afford functionalized decalins and hydrindane ring systems. The heterocyclic carbene-substituted ruthenium alkylidene **5** mediated the tandem reaction smoothly. It was found that the major side reaction, dimerization of the starting material, was suppressed by initially sparging the reaction with ethylene. Hydrindane ring formation proceeded at room temperature, while the decalin system required elevated temperature (Scheme 2.2-177) [262].

Blechert *Tetrahedron* **2002**, 58, 7503

Scheme 2.2-174

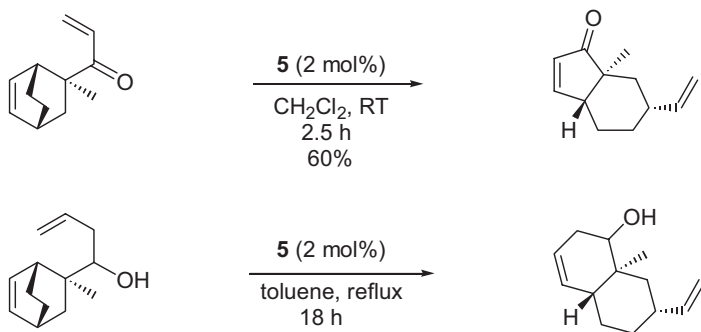
Blechert *JOC* **2002**, 67, 4325

Scheme 2.2-175

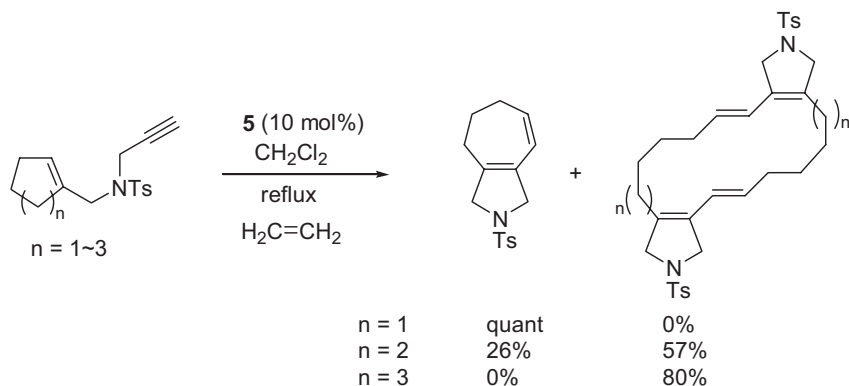
Grubbs *CC* **2001**, 2648

Scheme 2.2-176

Tandem ROM/RCM of 5-, 6-, and 7-membered cycloalkenynes bearing the alkyne moiety at the C-1 position was also demonstrated with catalyst **5** (Scheme 2.2-178) [263]. Under an atmosphere of ethylene, tandem ROM/RCM proceeded efficiently and bicyclic and/or dimeric compounds were obtained in good yields.

Phillips *TL* **2002**, 43, 5357

Scheme 2.2-177

Mori *OL* **2002**, 4, 3855

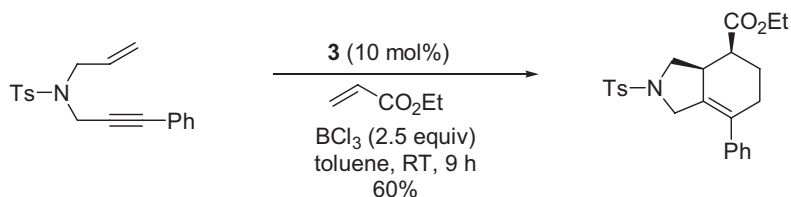
Scheme 2.2-178

2.2.12.2

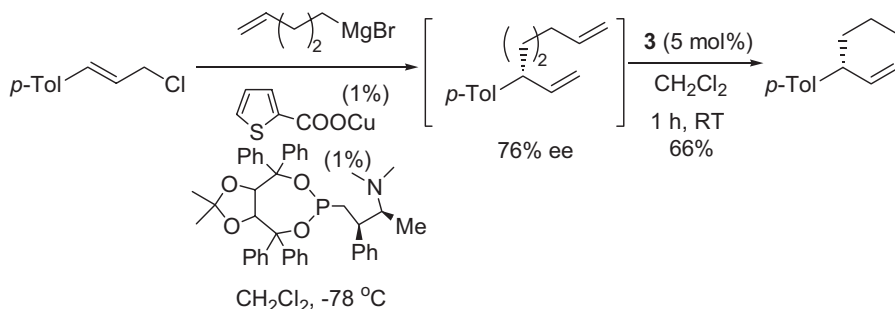
Other Tandem RCM

Pehydroindenes and pehydroisindoles were obtained with high efficiency by a one-pot, tandem enyne metathesis and Diels-Alder reaction (Scheme 2.2-179) [264]. The one-pot reactions proceeded with higher yields as compared to the stepwise sequence. It is notable that ruthenium catalyst **3** is compatible with various Lewis acids such as BCl_3 , $AlCl_3$, or $ZnCl_2$, which made the one-pot reactions possible.

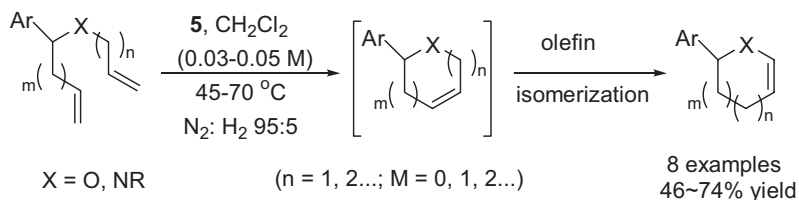
Alexakis recently disclosed tandem copper-catalyzed enantioselective allylation/RCM for the formation of carbocycles. This one-pot overall substitution-metathesis procedure proceeded smoothly, and the RCM product was obtained within 1 h at

Laschat *Synthesis* **2000**, 1766

Scheme 2.2-179

Alexakis *OL* **2002**, 4, 4147

Scheme 2.2-180

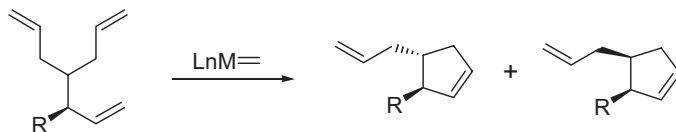
Snapper *JACS* **2002**, 124, 13390

Scheme 2.2-181

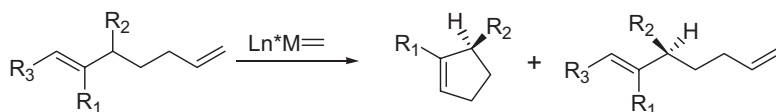
room temperature, with the same enantioselectivity as the intermediate diene (Scheme 2.2-180) [265].

Snapper synthesized several cyclic enol ethers through a tandem ruthenium-alkylidene-catalyzed ring-closing metathesis followed by a ruthenium-hydride-catalyzed olefin isomerization sequence from readily available acyclic dienes (Scheme 2.2-181) [266]. Because the tandem process enabled the formation of target molecules in two consecutive reactions by the same catalytic precursor in a single reaction pot, this process is particularly attractive to organic chemists.

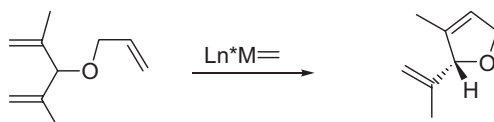
Diastereoselective Metathesis



Catalytic Kinetic Resolution



Catalytic Asymmetric Desymmetrization



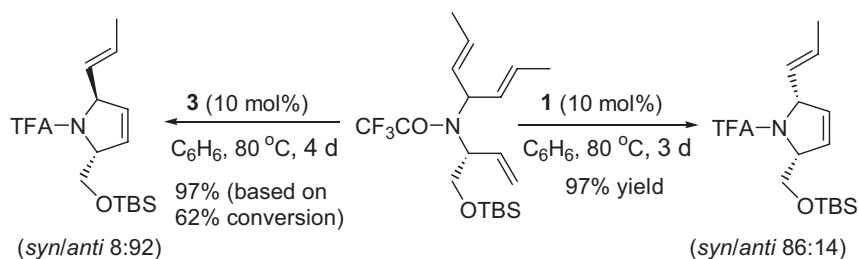
Scheme 2.2-182

2.2.13

Asymmetric RCM

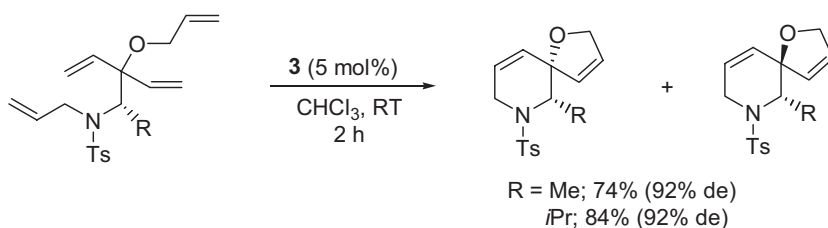
Although olefin metathesis mainly transforms olefins and alkynes into other alkenyl and alkynyl compounds, the reactions can be used for resolving or generating stereogenic centers in the products. According to the type of reactions, there are three stereoselective metathesis conversions (Scheme 2.2-182). If the substrate already has a stereogenic center(s) and metathesis selects only one olefin attached to the prochiral center, the produced compound would have additional stereocenters (diastereoselective metathesis). High selectivity can be obtained by the steric communication of the preexisting chiral center with the carbene complex. A second approach involves the kinetic resolution of acyclic dienes by chiral carbene complexes. A more attractive strategy for the stereoselective metathesis reaction is asymmetric desymmetrization of prochiral triolefinic substrates by chiral carbene catalysts, because that delivers the products with maximum yield (100% versus 50% in a typical kinetic resolution). These latter two strategies are covered in a following chapter (Chapter 2.3).

Blechert described the first example of a diastereoselective RCM reaction in which an existing chiral center controls the direction of cyclization of prochiral dienes [267, 268]. This strategy requires that initial metathesis occur at the double bond of the chiral center and that the olefins of the prochiral center do not react with each other. Blechert achieved this by a modification of the prochiral olefins



Blechert *ACIEE* **1996**, 35, 2376
Synthesis **1997**, 61

Scheme 2.2-183



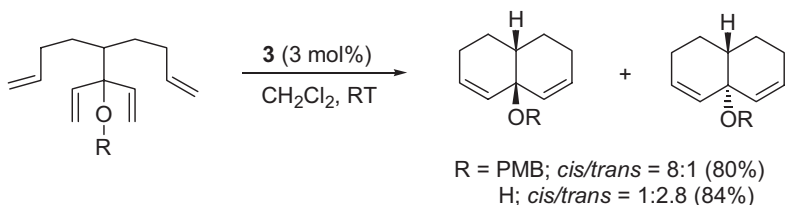
Wallace *TL* **2000**, 41, 2027

Scheme 2.2-184

from terminal to internal position so that the likelihood of ring closure between the sterically crowded double bonds at the prochiral center was minimized. RCM of the triene substrate with ruthenium catalyst **3** provided the *anti*-product with remarkably high selectivity, while the *syn*-isomer was preferentially produced in the presence of molybdenum catalyst **1** (Scheme 2.2-183).

An elegant example of diastereoselective double ring-closing metathesis reaction to afford a spirocyclic compound has been reported (Scheme 2.2-184) [269, 270]. This approach requires the existing stereocenter in the substrate to differentiate the diastereotopic vinyl group. The observed diastereoselectivity was remarkably high, and, more surprisingly, this value was not affected by the alkyl substituent in the substrate.

Lautens disclosed another example of a diastereoselective RCM reaction [271]. Although RCM of tetraenes with **3** (3 mol%) gave 7-membered cyclized diene as a major product (70%) under normal conditions, the same reaction with a higher loading of **3** (12 mol%) under an atmosphere of ethylene afforded bicyclic compound as a major product (Scheme 2.2-185). The stereochemistry of the produced bicycle was predominantly the *cis* relationship. However, RCM of tetraenyl alcohol gave the bicycle with the *trans* isomer predominating.



Lautens *AC/EE* **1999**, 38, 129

Scheme 2.2-185

2.2.14

Synthesis of Complex Molecules

2.2.14.1

Template-Directed RCM

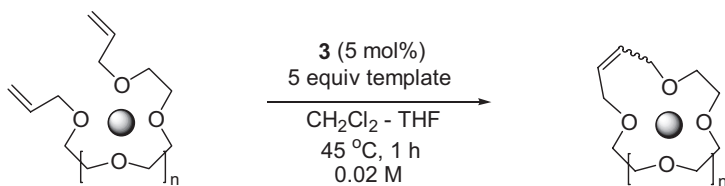
Because all RCM reactions are known to be influenced by several factors – including the kinetics of ring closing, ring strain, and competing metathesis-based polymerization – the close proximity of the olefins induced by the incorporation of conformational constraints into the substrates should be beneficial for the promotion of the desired RCM. Template-directed RCM utilizes non-covalent interactions between a diene and an appropriate template to enhance the RCM of linear dienes devoid of other conformational constraints. The metal ions capable of restricting the diene to a conformation favoring RCM give the highest yield of ring-closed product and also favor the formation of the *cis* isomer with an unsaturated crown ether analogue (Scheme 2.2-186) [272].

Metal-templated RCM reactions with palladium(II) and platinum(II) cation-bound diolefins were explored by van Koten (Scheme 2.2-187) [273]. The nature of the metal-to-ligand coordination bond is of crucial importance for the success of this type of ring-closure process. It must be sufficiently strong under the reaction conditions to prevent ligand dissociation, yet undergo facile dissociation after macrocyclization by cleavage of the metal-to-ligand interactions. The 3,5-disubstituted pyridine bound to an $\text{NCN-Pt}^{\text{II}}$ center underwent a fast metathesis reaction, whereas the same reaction with Pd^{II} was much slower with side reactions. Gladysz also extensively studied olefin metatheses in metal coordination spheres and developed a new versatile strategy for the construction of macrocyclic ligands by template-directed RCM using catalyst 3 [274] (see Chapter 2.11).

2.2.14.2

RCM in Supramolecular Chemistry

Catalytic RCM has been elegantly applied to the construction of fascinating molecular systems assisted by supramolecular arrays. The use of the extremely efficient and mild ruthenium-carbene catalyst in RCM permitted the easy preparation



$n = 1, 2$

($n = 1$)

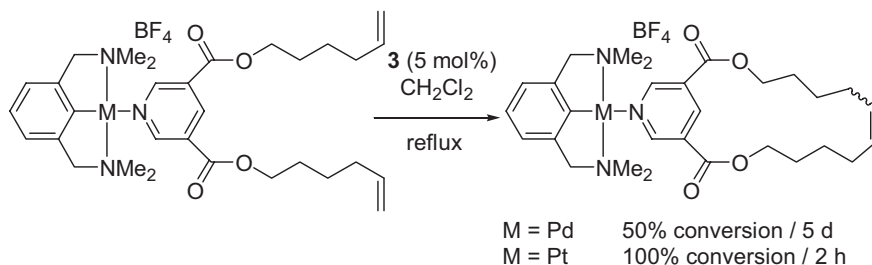
no template	39% (<i>cis/trans</i> 38:62)
LiClO_4	>95% (<i>cis/trans</i> 100:0)
NaClO_4	42% (<i>cis/trans</i> 62:38)
KClO_4	36% (<i>cis/trans</i> 36:64)

($n = 2$)

no template	57% (<i>cis/trans</i> 26:74)
LiClO_4	89% (<i>cis/trans</i> 61:39)
NaClO_4	90% (<i>cis/trans</i> 68:32)
KClO_4	64% (<i>cis/trans</i> 25:75)

Grubbs *ACIEE* **1997**, 36, 1101

Scheme 2.2-186



van Koten *ASC* **2002**, 344, 771

Scheme 2.2-187

of interlocked rings such as catenanes and rotaxanes, intertwined molecules such as knots, and dendrimer-typed molecules with respect to materials science and biologically applicable molecular machines and motors [275].

The synthetic approach utilizes a combination of a transition-metal-based template strategy and RCM to provide access to [2]catenanes and trefoil knots as summarized in Figure 2.2-4 [276, 277]. The formation of an intertwined complex of two diolefin molecules with a transition metal followed by twofold RCM using a ruthenium catalyst and decomplexation gives a [2]catenane (Figure 2.2-4a). Similarly, the knot can be produced by first allowing two coordinating fragments to gather and interlace around two transition metal centers. The RCM reaction of the metal complex bearing terminal olefins with a ruthenium catalyst furnishes the dimetal knot. Sequential reduction and decomplexation of the product affords a

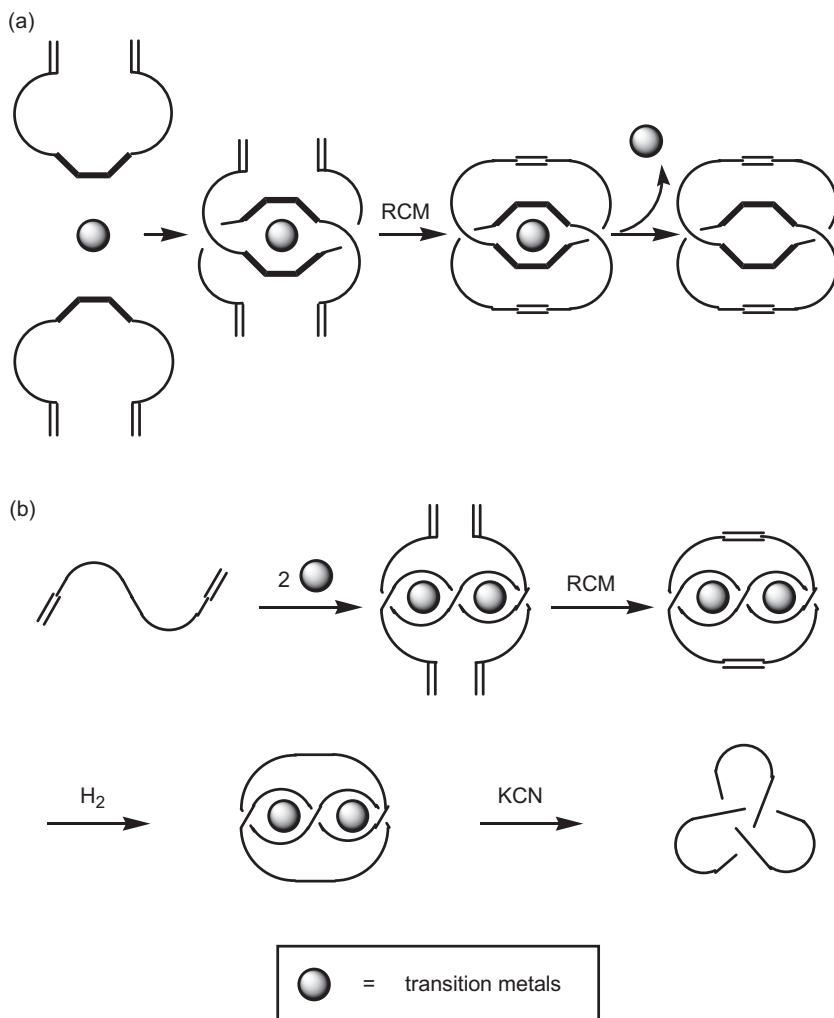
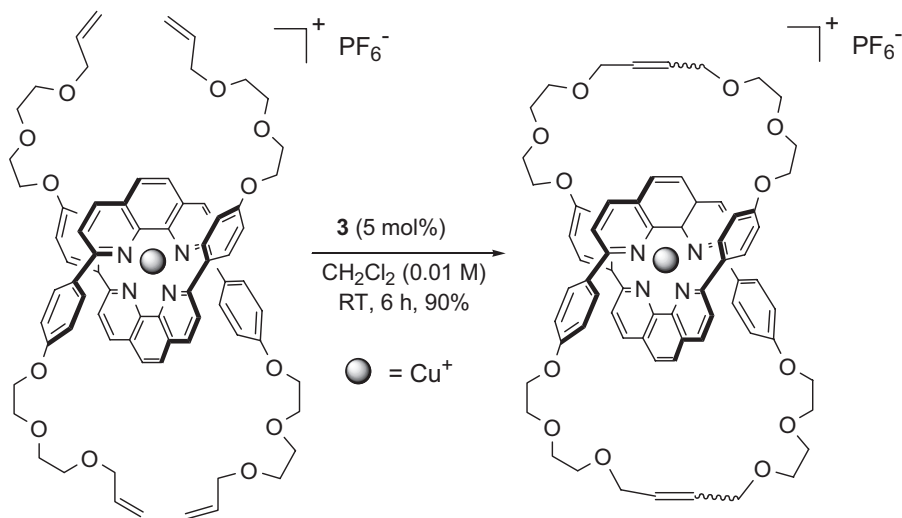


Fig. 2.2-4. Schematic drawing: (a) formation of catenanes, (b) formation of trefoil knots.

trefoil knot isomer (Figure 2.2-4b). Application of the reversible C=C forming RCM to the field of supermolecules signifies a spectacular synthetic improvement in both yield and experimental conditions for the synthesis of interesting molecules such as catenanes, rotaxanes, knots, and dendrimers.

A large number of substituents have been introduced into the supermolecules to enable these compounds to act as a molecular machine by an oxidation/reduction process, electrochemically/photochemically triggered molecular motion, or acid/base-induced electron transfer. The use of a template is crucial for the construction of a supramolecular-assisted molecular system. Grubbs and Sauvage reported the synthesis of catenanes by the combination of template effects and intramolecular



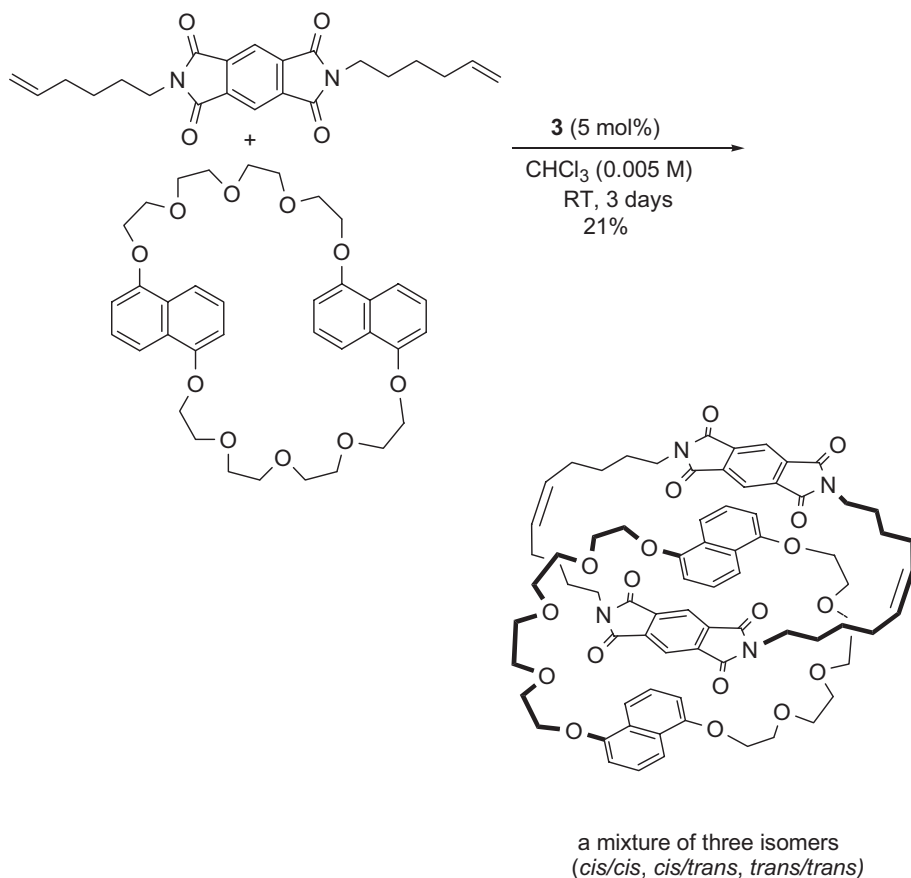
Grubbs *ACIEE* **1997**, 36, 1308
JOC **1999**, 64, 5463

Scheme 2.2-188

RCM reaction of the resulting phenanthroline-based ligands as shown in Scheme 2.2-188 [276, 278]. A copper-chelated tetra-olefinic complex was cleanly cyclized by RCM using ruthenium catalyst **3** to form a two 32-membered catenane in an excellent yield.

Sanders reported the synthesis of neutral π -associated [2]catenanes by RCM of π -electron-deficient aromatic diimides containing olefin-terminated alkyl chains in the presence of a π -electron-rich dinaphtho crown ether under thermodynamic control. Templating π -donor/ π -acceptor interactions favored production of the more thermodynamically stable catenane products (Scheme 2.2-189) [279]. The two molar equivalents of diimide were combined with the dinaphtho crown ether in chloroform to form the donor-acceptor complex. The complex was then subjected to the RCM reaction by addition of ruthenium carbene catalyst **3** to afford the corresponding [2]catenane as a mixture of three alkene isomers in 21% yield.

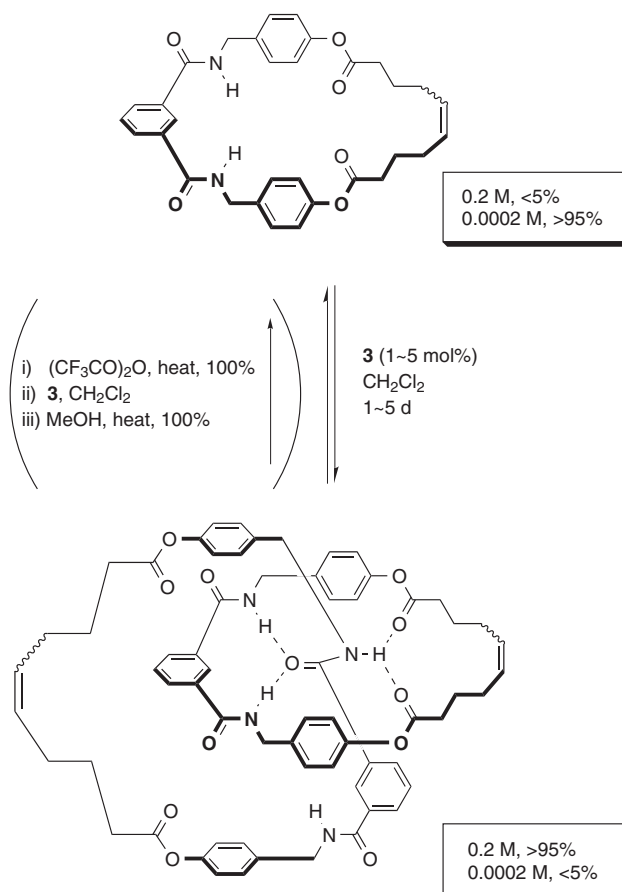
Leigh disclosed an organic “magic ring” formation reaction of benzylic amide macrocycles and [2]catenanes by reversible ring-opening and -closing reactions using ruthenium catalyst **3** via the hydrogen bond-directed assembly/disassembly of catenanes under thermodynamic control (Scheme 2.2-190) [280]. The unlocked component, an isophthaloyl benzylic amide macrocycle, possessing an internal olefin self-assembled via interlocking to afford isomeric [2]catenanes in a 95% yield at equilibrium at 0.2 M concentration. Alternatively diluting the ring-opening and -closing reaction mixture or “switching off” by reversible trifluoroacetylation of the amides converted the catenane back to the simple macrocycle. At concentrations of 0.0002 M or less, the presence of only the simple macrocycle was observed.

Sanders *NJC* **1998**, 1019

Scheme 2.2-189

Leigh later reported the synthesis of octahedrally coordinated benzylic imine catenanes using RCM in the presence of a range of different metal complexes of the same ligand (Scheme 2.2-191) [281]. Synthesis of the octahedral catenanes was appealing due to their higher oxidation state compared with tetrahedral catenanes in redox-switchable systems. The benzylic imine catenanes were synthesized by the double macrocyclization of a preformed octahedral complex by the RCM reaction. Even though imines were known to be incompatible with olefin metathesis, the metal pre-coordinated imines smoothly underwent double macrocyclization by RCM. Thus, this simple and effective synthetic route to octahedral coordination could possibly be extended to the synthesis of other interlocked-type architectures.

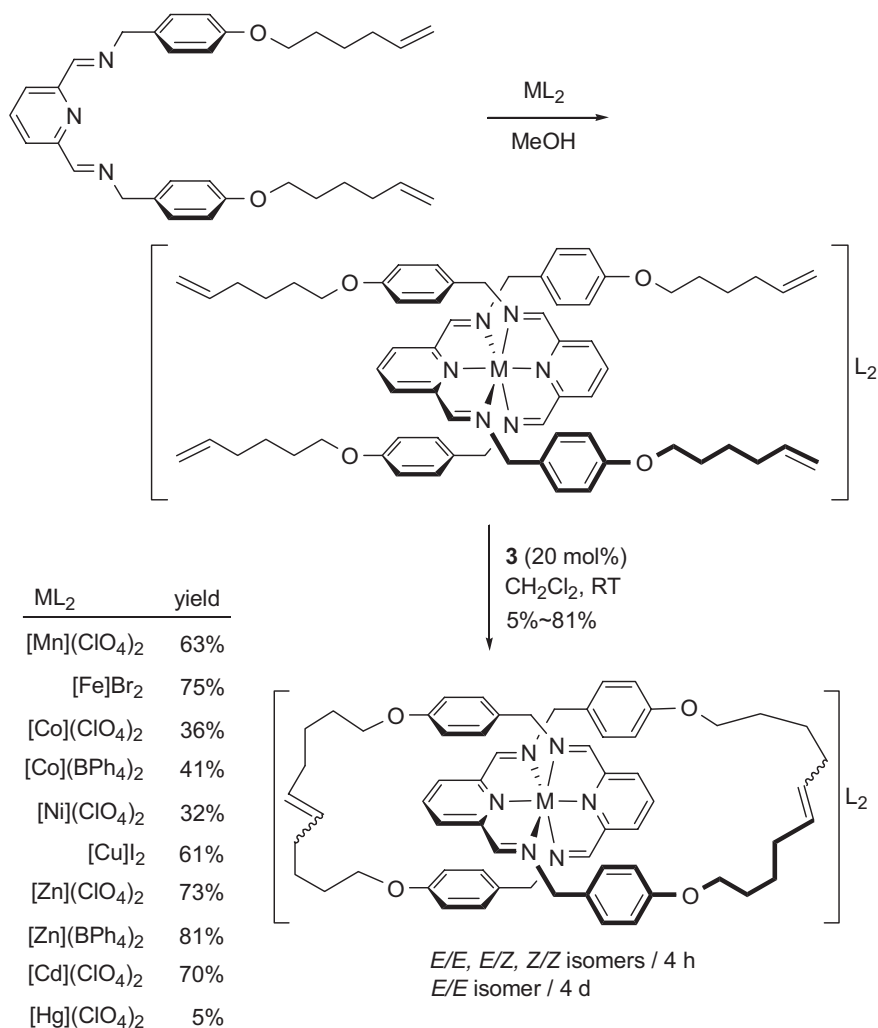
The cationic, neutral, or anionic template methodology for the construction of macrocycles and supramolecular arrays facilitated the synthesis of complexed



Leigh *JACS* **1999**, *121*, 1599

Scheme 2.2-190

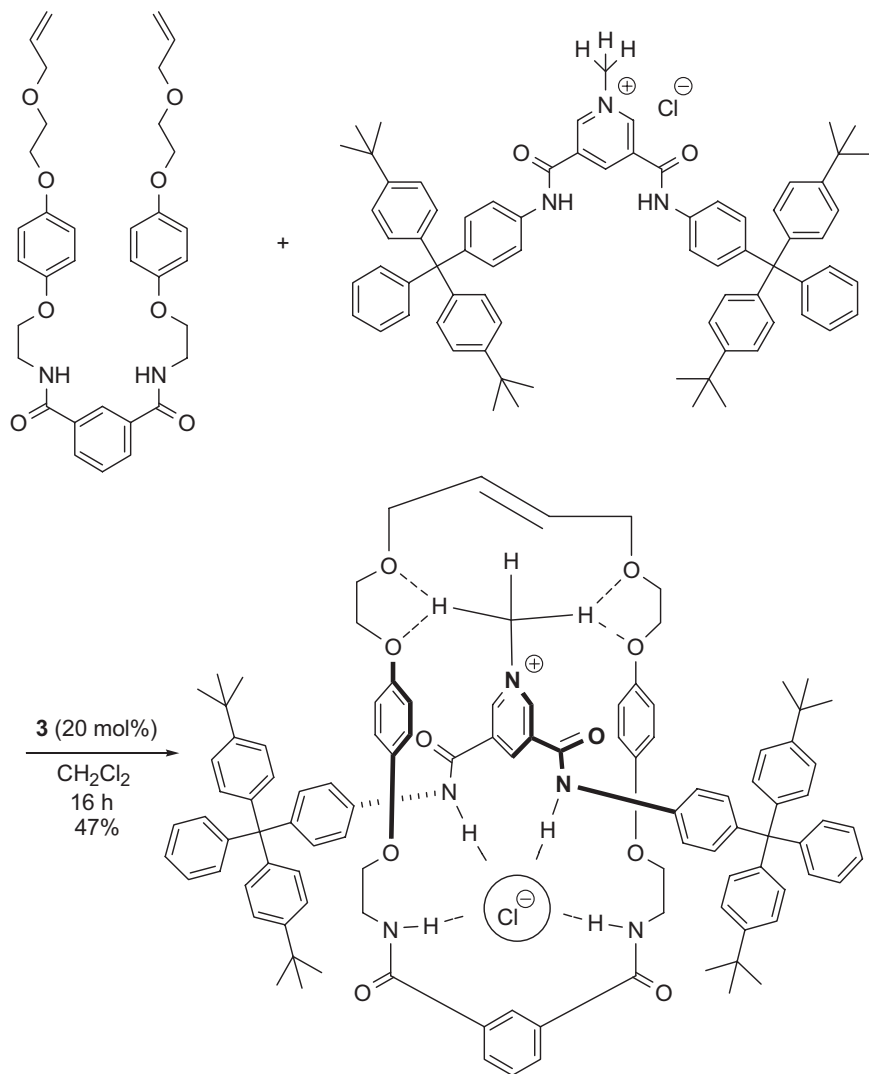
molecules by a variety of non-covalent forces such as metal coordination, hydrogen bonding, π - π stacking, and solvophobic interactions. However, examples of anionic templates in the field of supramolecular chemistry are rare because of the relatively small ratio of charge to radius and sizable solvation energy. There are only a few instances of template synthesis employing anions in the construction of mechanically bonded compounds [282]. Beer recently reported a chloride-anion-templated [2]rotaxane formation using RCM [283]. He elegantly synthesized the [2]rotaxane with the RCM-assisted “clipping” method instead of utilizing the generally accepted “stoppering” method of the terminal groups of a preformed pseudorotaxane (Scheme 2.2-192). The electron-rich hydroquinone in the pendant arms of the hydrogen-bond-donating ligand engaged the electron-poor pyridinium ring by a classic donor-acceptor π -stacking interaction and thus aided the complexation of

Leigh *ACIEE* **2001**, 40, 1538

Scheme 2.2-191

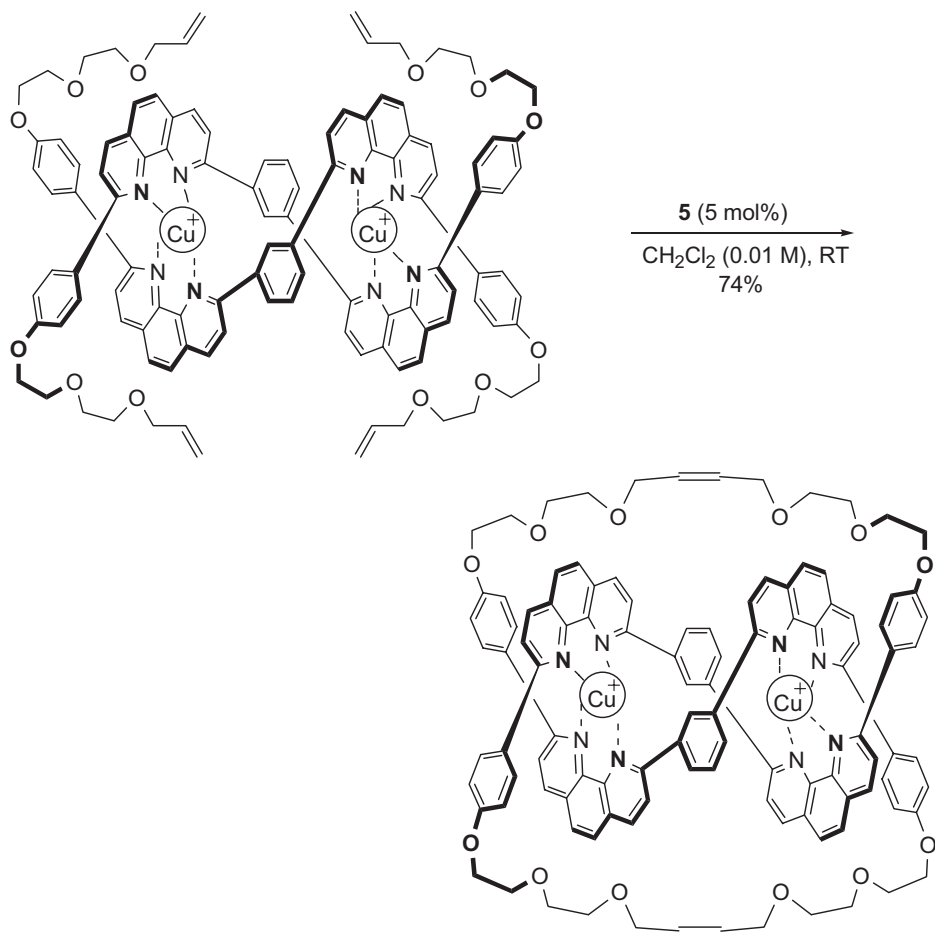
the chloride anion template. The proximity of the allylic end groups of the ligand around the dumbbell-shaped complex supported the anion template to facilitate the RCM about the ion pair to produce the anion-templated [2]rotaxane in moderate yield.

Sauvage efficiently synthesized a phenanthroline-based molecular knot in good yield by copper(I)-induced formation of a double-stranded helix bearing four terminal alkenes followed by ruthenium(II)-catalyzed RCM (Scheme 2.2-193) [284]. Because both right-handed and left-handed helical intermediates are equally

Beer *JACS* **2002**, *124*, 12469

Scheme 2.2-192

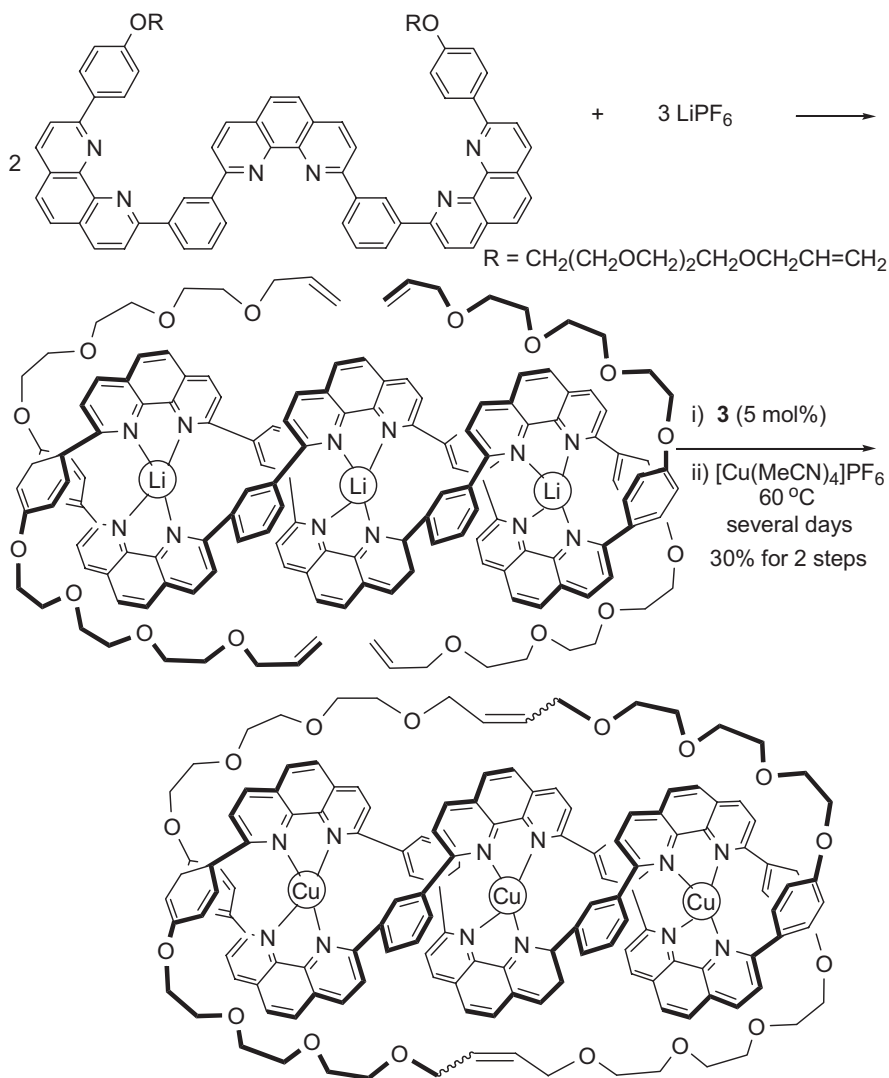
avored in the absence of any chiral induction, a racemic mixture is formed prior to cyclization of the terminal olefins, and thus the resulting trefoil knot exists as a racemate. The key features for the formation of the copper(I)-complexed 82-membered knotted ring were the quantitative formation and high stability of the dicopper-mediated helical precursor of bisphenanthroline units with 1,3-phenylene linkers as well as the smooth intramolecular macrocyclization via the RCM.



Sauvage CC 1997, 2053

Scheme 2.2-193

Lithium-templated synthesis of doubly interlocked [2]catenanes was reported as the first example of the use of alkali or alkaline-earth cations via RCM. The catenane synthesis of the two linear coordinating fragments, each containing three 1,10-phenanthroline units, was achieved by the efficient RCM reaction (Scheme 2.2-194) [285]. The two tris-chelating ligands were incorporated with three lithium cations to afford double-stranded helical complex isomers containing six 1,10-phenanthroline units. The double cyclization by the RCM reaction using ruthenium catalyst **3** produced the 4-crossing [2]catenanes. The lithium-complexed catenane was converted slowly to the copper-complexed catenane in the presence of $[Cu(MeCN)_4]PF_6$ at 60 °C.

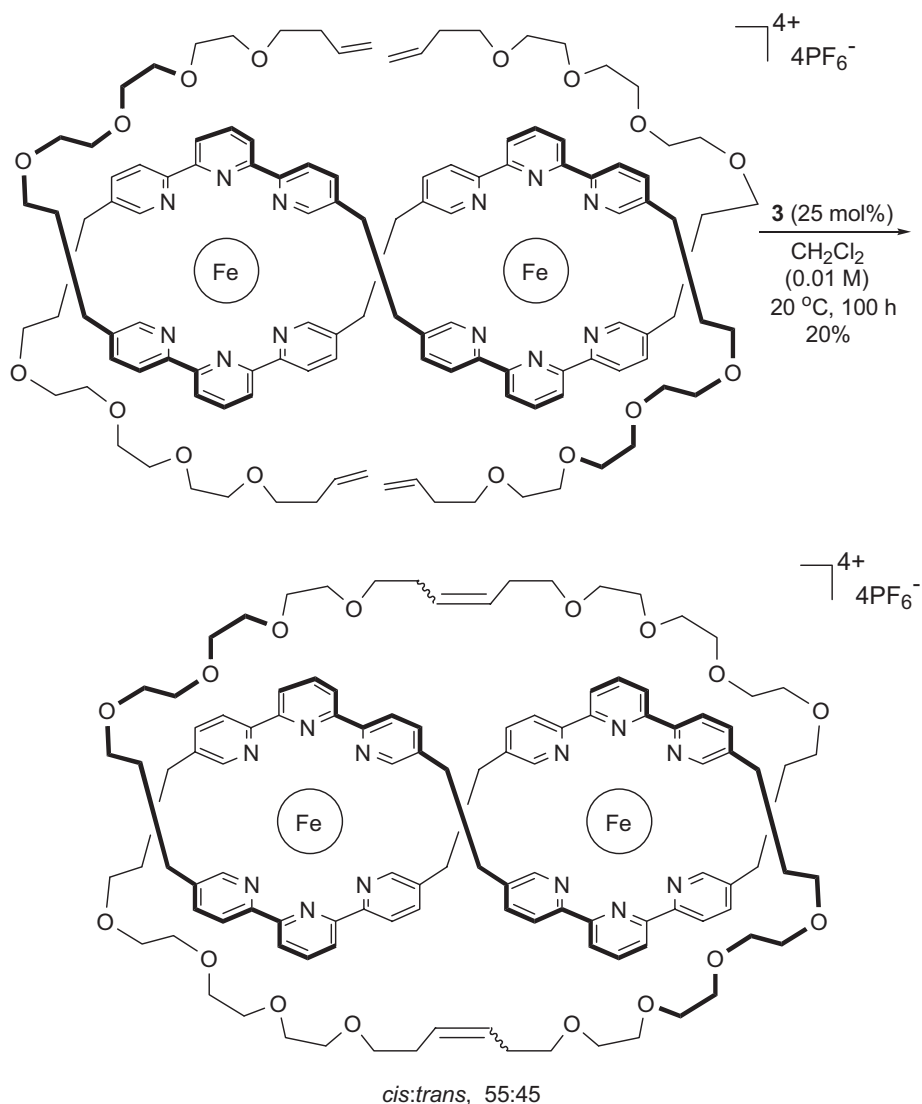


Sauvage CC 1999, 615

Scheme 2.2-194

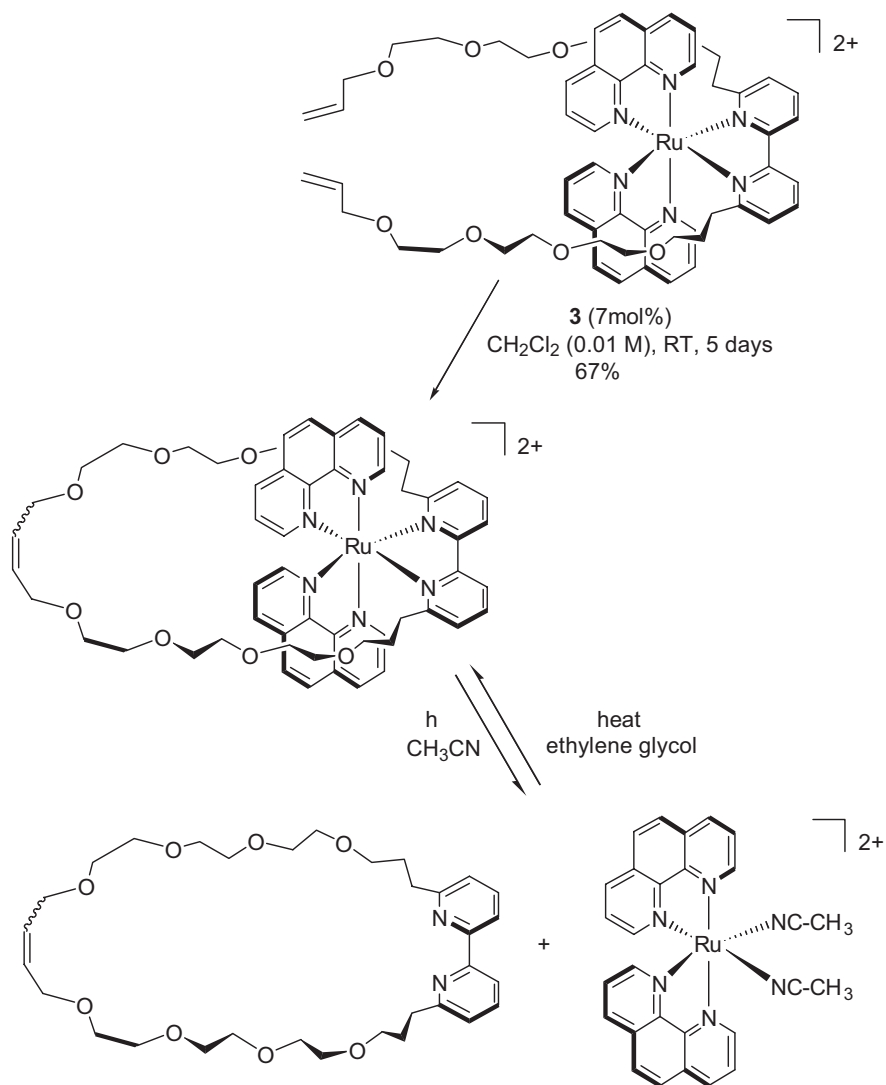
An iron(II)-templated synthesis of molecular knots containing two tetrahedral or octahedral coordination sites was also reported in a similar situation [277]. The successful synthesis of terpyridine-based diiron(II) molecular trefoil knots was observed for the first time by using iron(II) as a highly efficient template in RCM (Scheme 2.2-195)

Molecular assemblies such as molecular machines or motors are usually set into

Savage *JACS* **1999**, *121*, 994

Scheme 2.2-195

motion by chemical or electrochemical signals and by photochemical excitation. Sauvage reported a photochemically induced movement of a molecule based on dissociative photoexcited states (Scheme 2.2-196) [286]. The macrocyclic complex was prepared from the corresponding ruthenium precursor via RCM using catalyst **3**. When the RCM product was irradiated with light ($\lambda > 300\text{ nm}$), it expelled the ruthenium bisphenanthroline unit from the macrocyclic complex, whereas the

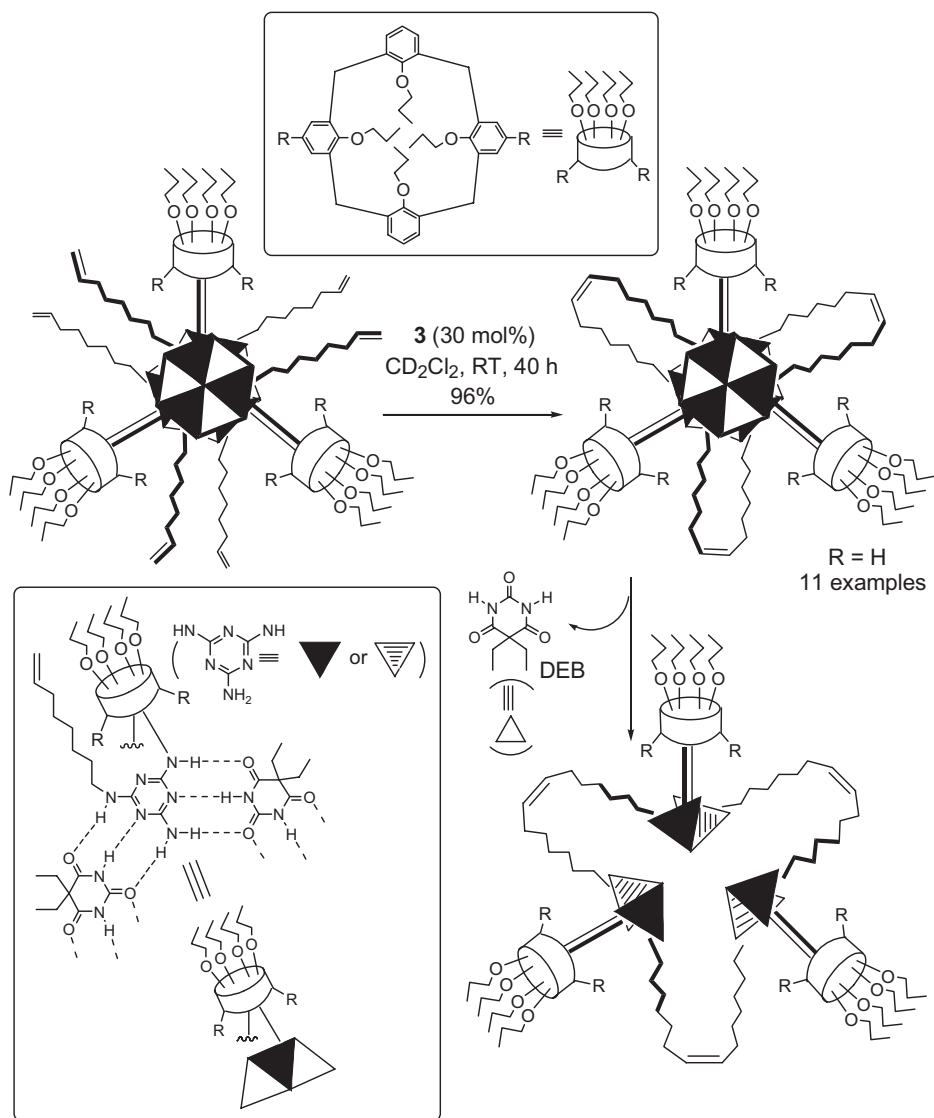
Savage *NJC* **2001**, 25, 22

Scheme 2.2-196

thermal backward reaction resulted in re-coordination of the two species efficiently and quantitatively.

Because dynamic combinatorial chemistry implements the reversible connection of sets of basic components to give access to a dynamic library, dynamic combinatorial libraries have attracted much attention [287, 288]. Most libraries are based on the reversible formation of either covalent or coordinative bonds. Reinhoudt

reported the covalent capture of dynamic hydrogen-bonded assemblies by RCM, which converted the dynamic assemblies into covalent analogues that could be readily characterized. The threefold RCM reaction of the assembly, which was compatible with the hydrogen-bonded network in the assembly bearing oct-7-enyl side chains, afforded covalent linkage of the three calix[4]arene in excellent yield (Scheme 2.2-197) [289, 290]. The RCM did not proceed in the absence of 5,5-



Reinhoudt CC 2000, 367
CEJ 2002, 8, 2302

Scheme 2.2-197

diethylbarbituric acid in the reaction media. The MALDI-TOF mass spectrometry of the resulting covalently captured hydrogen-bonded assemblies, which lost a diethylbarbituric acid moiety as expected during the mass operation, clearly proved the efficient formation of the desired RCM product.

Zimmerman synthesized dendrimers with internal cross-links by RCM using catalyst **3** in excellent yield (Scheme 2.2-198) [291, 292]. After RCM the ruthenium catalyst was removed by treating with tris(hydroxymethyl)phosphane and silica. Purification by preparative size-exclusion chromatography afforded the cored dendrimers in excellent yield. Hydrolysis of the RCM product led to complete core removal.

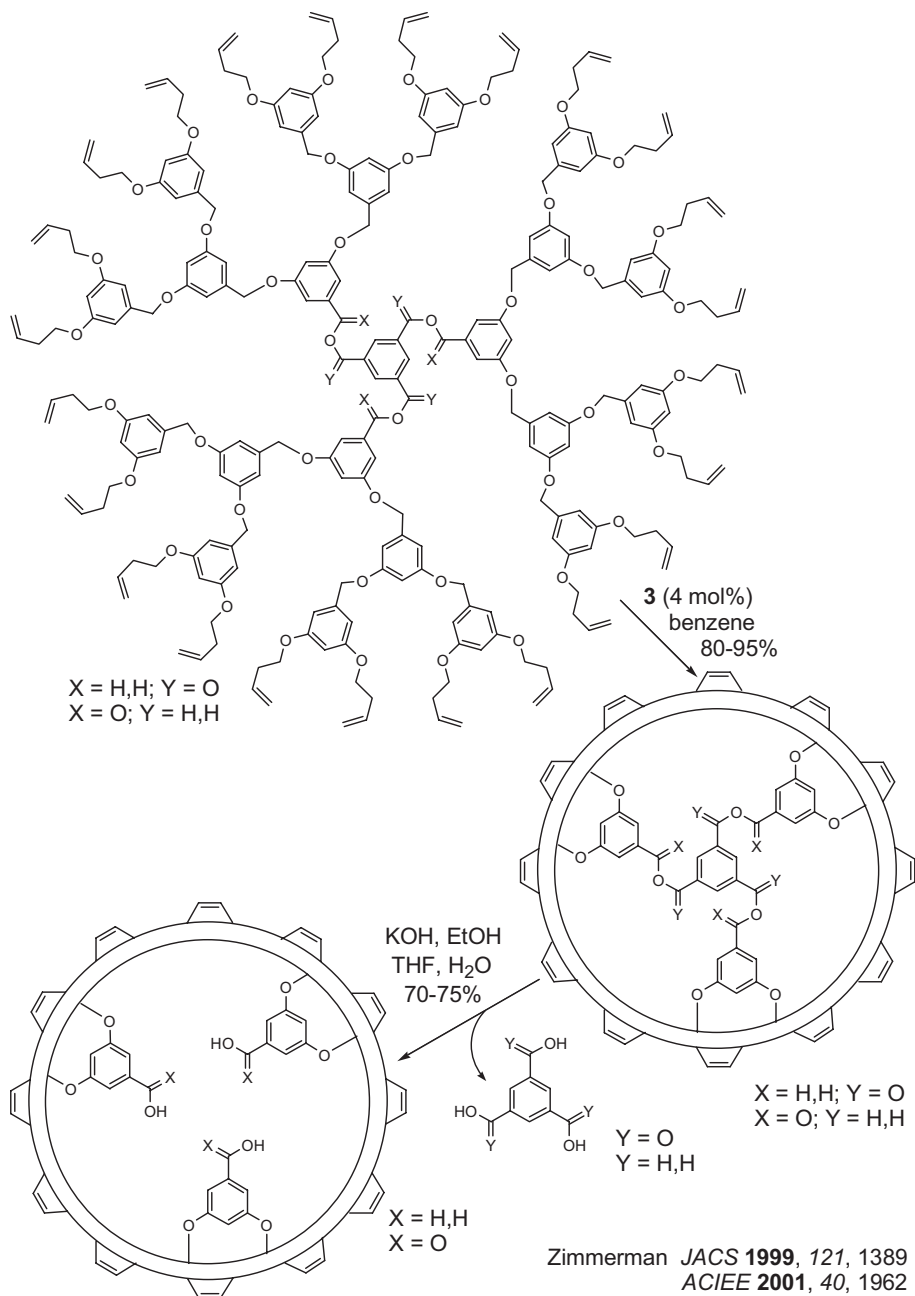
Zimmerman elegantly utilized the RCM reaction to prepare synthetic host systems capable of selectively binding guest molecules. The dynamic imprinting of dendritic macromolecules with porphyrin templates yielded synthetic host molecules containing one binding site each. Thus, the porphyrin core dendrimer was cross-linked using 4 mol% catalyst per alkene via RCM. Ester hydrolysis of the resulting porphyrin template enabled the removal of the core porphyrin from the macrocycle in moderate yield (Scheme 2.2-199) [293].

To generate complex and ingenious architectures, supramolecular chemistry relies upon self-assembly processes that exploit the reversibility inherent in the formation of non-covalent bonding interactions, thereby allowing a system to strive for – and eventually attain – a thermodynamic minimum. The RCM reaction is also a reversible process, but it results in the formation of covalent, rather than non-covalent, bonds, thus allowing for the formation of more robust structures, i.e., molecules rather than delicate supermolecules. This common element of reversibility, therefore, introduces a certain degree of compatibility between RCM and supramolecular chemistry and – in addition to the mild conditions under which C=C olefin metathesis can be performed – has resulted in the union of these two areas in order to create novel interlocked and intertwined structures. The few examples discussed in this section provide a glimpse of the potential for this marriage and may herald an exotic and diverse future for this field – one that may lead from interlocked structures, to molecular machines, to molecular logic, and, ultimately, to molecular computation.

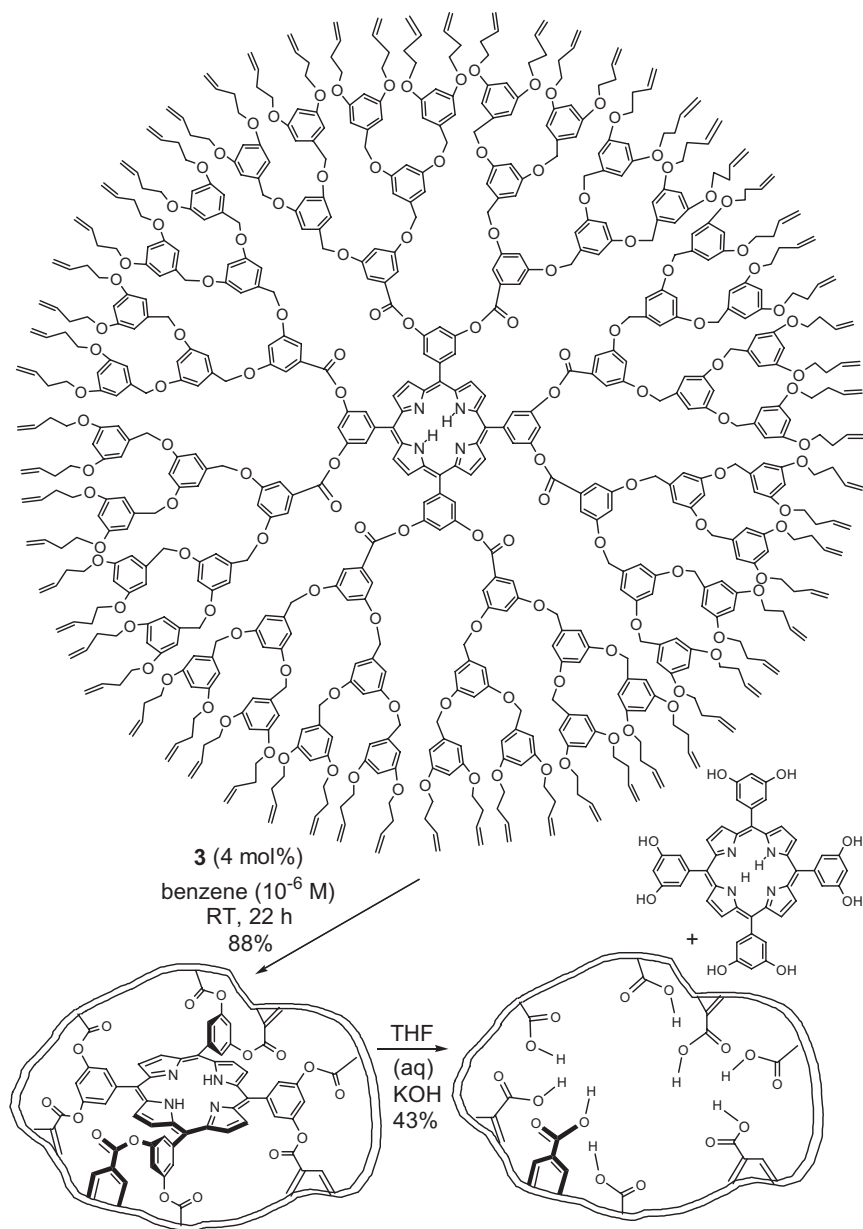
2.2.14.3

Synthetic Applications

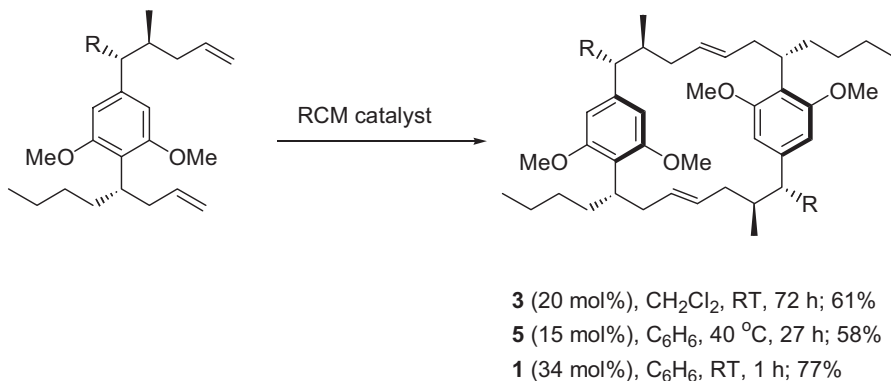
The rapidly emerging RCM reaction has found many spectacular applications in the synthesis of complex molecules. Among many examples, dimerization of molecules via C–C bond formation can serve as an elegant means for the generation of architecturally complex compounds. Intermolecular double olefin metathesis of dialkenyl moieties was used by Smith to assemble the key molecular skeleton of (–)-cyclidrocyclophanes **A** and **F** in a significantly impressive fashion (Scheme 2.2-200) [294, 295]. Dimerization was affected by three carbene complexes almost in similar efficiency to afford the “head-to-tail” dimer in modest yields. It is noteworthy that the alternative “head-to-head” dimer was not detected in these experi-



Scheme 2.2-198

Zimmerman *Nature* **2002**, 418, 399

Scheme 2.2-199

Smith III *JACS* **2000**, 122, 4985

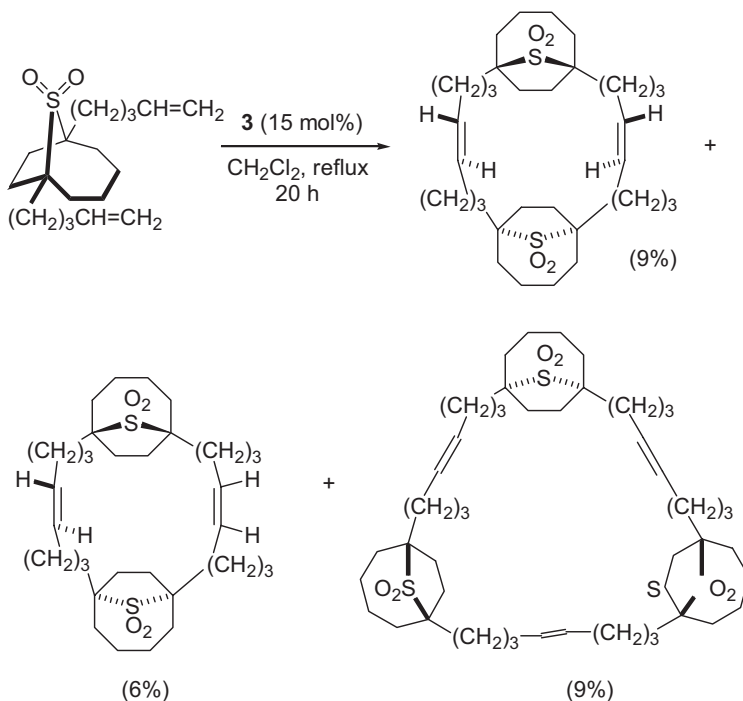
Scheme 2.2-200

ments regardless of the catalysts employed. This result presumably originated from the reversible nature of the metathesis reactions and the low-energy nature of the all-*trans* “head-to-tail” dimer.

Paquette used an RCM strategy for the construction of stereochemically defined polybicyclic molecules, paddlanes, starting from disubstituted bicyclic sulfones (Scheme 2.2-201) [296]. The sulfone group was considered as a key center to drive the ring-closure reaction forward by coordination to the ruthenium metal center of the catalyst. Reaction of the diolefinic sulfone with **3** afforded two dimeric compounds and a trimer in addition to oligomers. This ligation was considered an important driving factor for the overall reaction in that it served to maximize the unfavorable non-bonded steric interactions when the sulfone bridges adopted a *syn* relationship.

Schreiber reported that RCM could be utilized as a powerful means for split-pool syntheses of stereochemically and structurally diverse compounds [297]. RCM reactions of the amide precursors were effected by **3** under highly dilute concentrations to produce the 12-membered rings in moderate to excellent yields, together with varying amounts of 24-membered cyclic dimers (Scheme 2.2-202). Solid-structure analyses showed that the macrocyclic products adopt the idealized hexagonal conformations in most cases. It was also shown that the solid-phase approach is possible for bead arraying and compound distribution systems.

Fürstner described a highly efficient entry into the resin glycoside family of natural products by the action of RCM for the formation of their macrolactone substructures [298]. Reactions of fully functionalized trisaccharide dienes with the ruthenium catalyst and subsequent hydrogenation of the resulting mixture of cycloalkenes afforded protected glycolipid tricolorin G in remarkable yield (Scheme 2.2-203). In addition, various analogues of this naturally occurring glycolipid have been obtained in a straightforward manner with the help of RCM reaction.

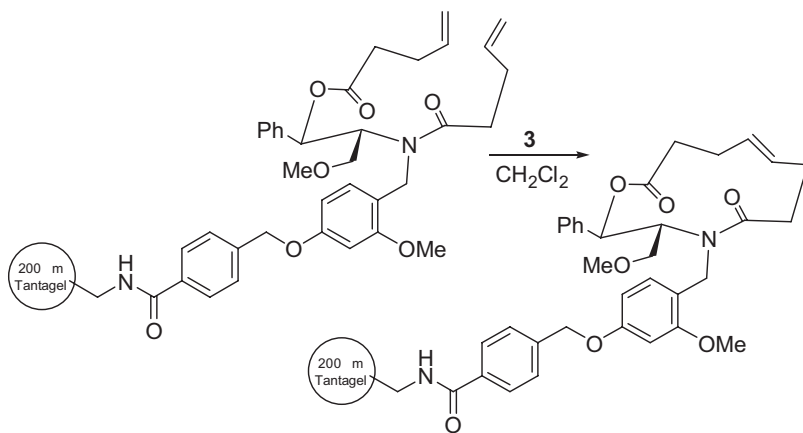
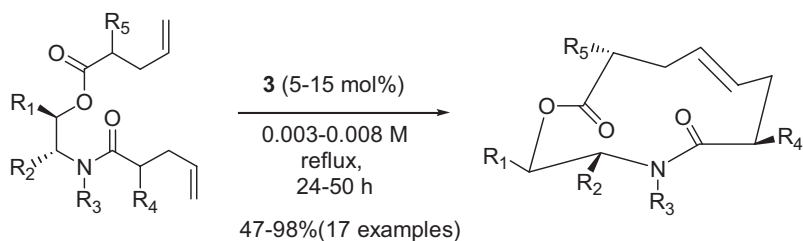
Paquette *JACS* **2000**, 122, 3391

Scheme 2.2-201

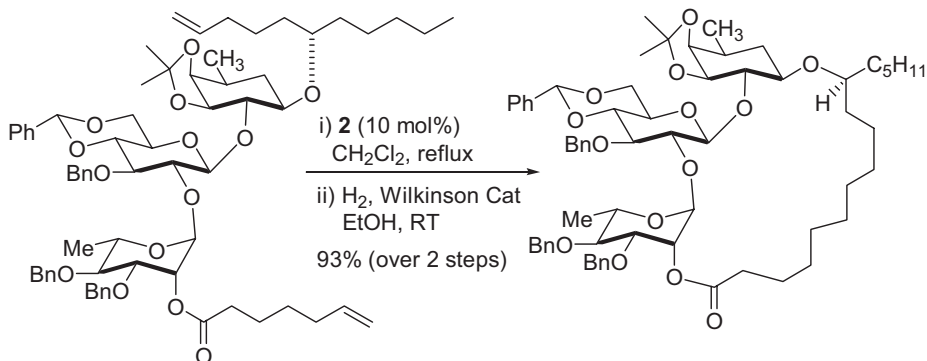
Georg reported the synthesis of a fully substituted macrocyclic core of salicylihalamide via an RCM reaction (Scheme 2.2-204) [299]. Salicylihalamides are naturally occurring cytotoxic macrolides and represent the first examples of macrolides having in common the salicylic acid moiety and an unsaturated enamide side chain. Readily available diacetone-D-glucose was used as the starting chiral synthon. The TBDMS protection of the phenolic alcohol was necessary for the desired *E*-alkene formation as the major product during the RCM reaction. When the phenolic moiety was intact, the RCM reaction provided the *Z* isomer as the major reaction product (*E*:*Z* 15:85, 60%). The sterically bulky TBDPS protecting group was considered to promote a conformational change in the transition state of the RCM that preferred the *E*-alkene production.

Epothilones A, B, and E are a class of 16-membered lactones that exhibit highly potent antitumor activity (Scheme 2.2-205) [300]. In addition to their interesting mechanism of biological action, their rather simple macrolactone structure has attracted considerable synthetic efforts heavily based on RCM strategy.

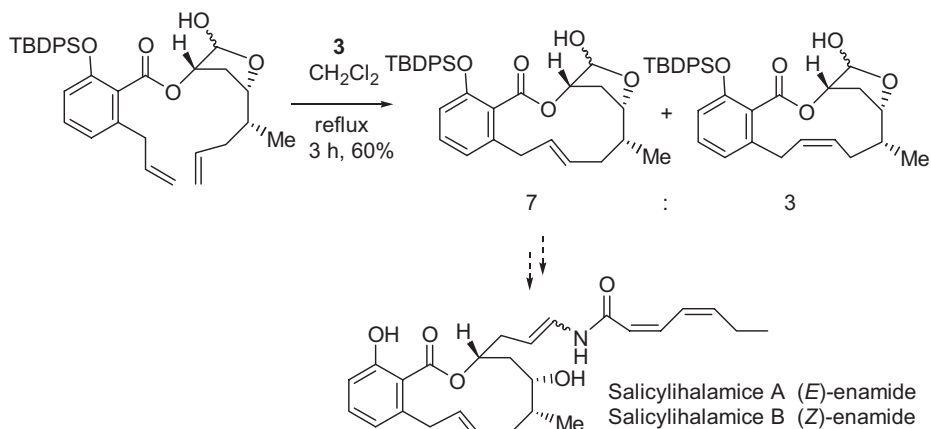
Nicolaou reported the first RCM-based studies on the synthesis of the macrocyclic skeleton of the epothilones [301–304]. The olefin metathesis reaction of an

Schreiber *JACS* **1999**, 121, 10648

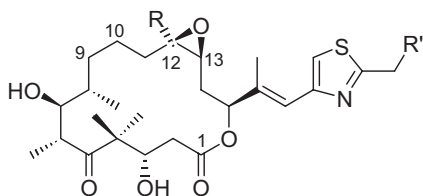
Scheme 2.2-202

Fürstner *JACS* **1999**, 121, 7814

Scheme 2.2-203

Georg CC **2001**, 255

Scheme 2.2-204

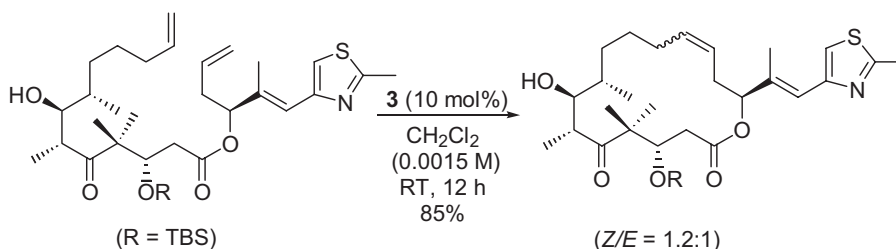
Hofle *ACIEE* **1996**, 35, 1567

Scheme 2.2-205

acyclic diene having an unprotected hydroxyl group at C7 was effected by Ru catalyst **3** in dilute methylene chloride to afford the 16-membered lactone with a mixture of two isomers (Scheme 2.2-206). It is interesting that the flexibility in the synthesis of the isomeric macrolides by RCM was claimed to potentially allow the generation of a diverse library of epothilones for further biological investigations.

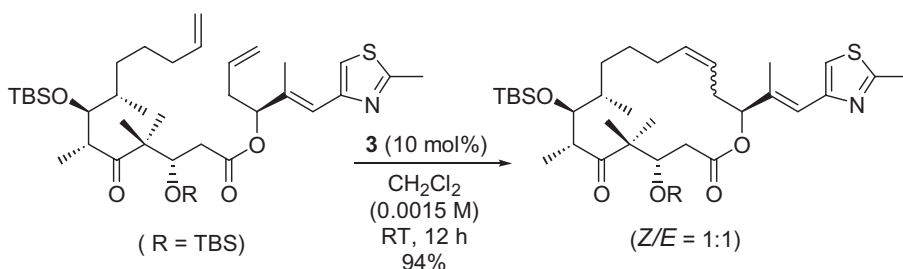
Schinzer reported another approach to the synthesis of epothilone in which RCM was also employed as a key step (Scheme 2.2-207) [305]. Almost the same strategy was used as in the Nicolaou synthesis; site of the metathesis also chosen to generate the $\Delta^{12,13}$ double bond. The C-7 hydroxyl group, in this case, was protected with TBS, and RCM of the diene precursor gave the cyclic epothilone A intermediate in excellent yield by the action of **3**.

With the C-12,C-13 disconnection producing an effective approach to epothilone A, it would seem likely that a similar strategy could be extended for the formation of epothilone B. Danishefsky demonstrated that RCM of a diene precursor bearing the C-12 methyl group did not proceed with the ruthenium catalysts, whereas the more active molybdenum carbene **1**, provided the 16-membered macrolide



Nicolaou *ACIEE* **1996**, 35, 2399
JACS **1997**, 119, 7960
ACIEE **1997**, 36, 166
ACIEE **1998**, 37, 84

Scheme 2.2-206



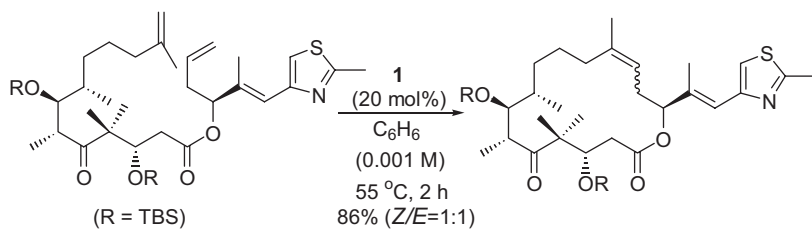
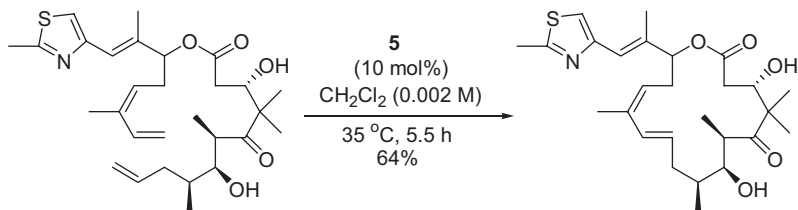
Schinzer *ACIEE* **1997**, 36, 523

Scheme 2.2-207

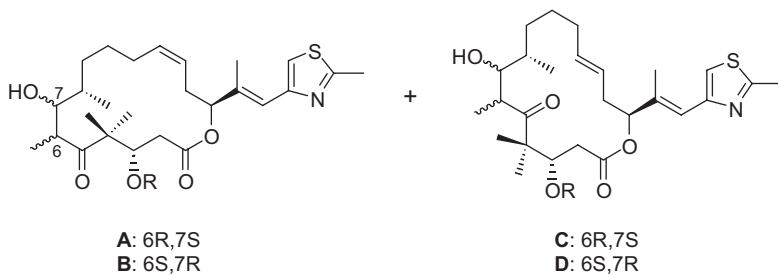
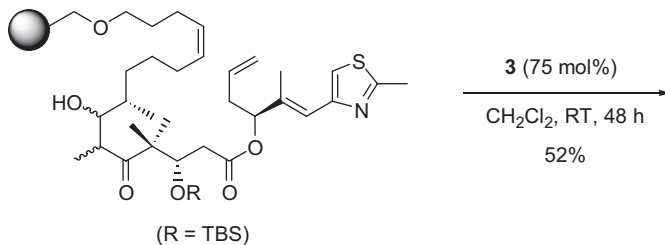
in good yield (Scheme 2.2-208) [306, 307]. In a newer approach, the same group explored RCM reaction with ruthenium catalyst **5** for the construction of 10,11-olefin in a stereospecific way, with the problematical Z -12,13-olefin geometry already in place. Catalysts **1** and **3** did not give RCM products as expected in this case [308, 309].

Nicolaou reported a solid-phase synthesis of epothilone A and its various derivatives by incorporation of a cyclization/cleavage strategy (Scheme 2.2-209) [310]. Upon treating solid-support-bound diolefinic substrate with 0.75 equivalent of ruthenium catalyst **3**, four diastereomeric products of the 16-membered lactone were released from the resin in 52% yield.

Manzamine A and ircinal A, which is a biosynthetic precursor of manzamine A, are a family of structurally complex indole alkaloids that exhibit potent antitumor activity. Their combination of unusual and complex polycyclic structure and their biological activity of the alkaloids have served as a challenging compound to test the feasibility of RCM. Several model studies have revealed that the 13-membered E ring and 8-membered D ring can be readily accessed by this ring-formation method. RCM-based total synthesis of ircinal A has been accomplished by Martin

Danishefsky *JACS* **1997**, 119, 2733Danishefsky *JACS* **2002**, 124, 9825

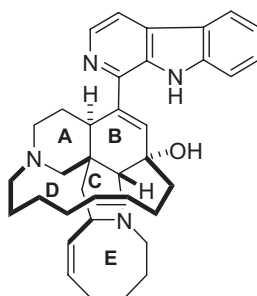
Scheme 2.2-208



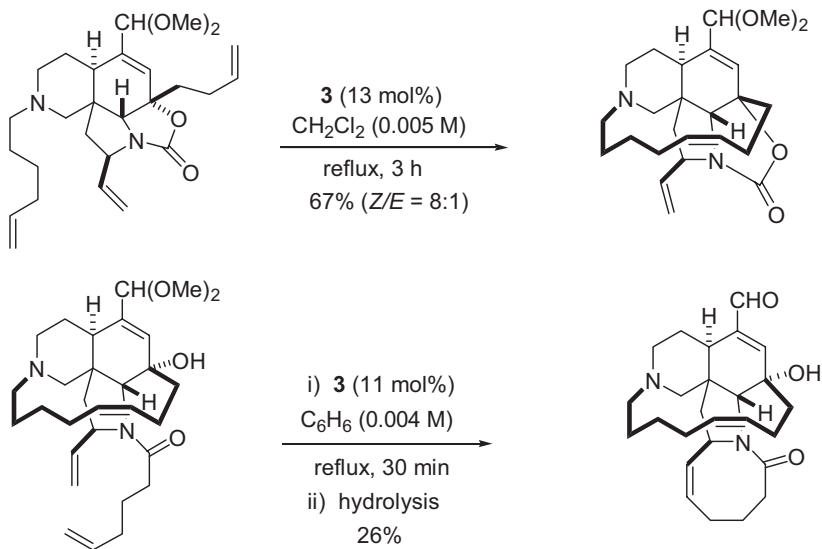
(A:B:C:D = 3:3:1:3)

Nicolaou *Nature* **1997**, 387, 268

Scheme 2.2-209



Manzamine A



Martin *JACS* **1999**, 121, 866
JACS **2002**, 124, 8584

Scheme 2.2-210

[311, 312]. Recently, the enantioselective total synthesis of manzamine A was reported by the same group [313]. Two sequential RCM reactions were exploited to elaborate the required 13- and 8-membered rings in the approach (Scheme 2.2-210). The first RCM for the formation of the D ring was carried out under high dilution concentrations by the action of **3** without need to protonate the tertiary amine. The 13-membered ring was formed in a 67% yield as a mixture of geometric isomers. Although the second ring closure turned out to be more sluggish compared to the first RCM, the total synthesis was completed by the formation of the 8-membered D ring with the action of **3** (26% yield).

References

- GRUBBS, R. H.; PINE, S. H. In *Comprehensive Organic Synthesis*; TROST, B. M.; FLEMING, I.; PAQUETTE, L. A., Eds.; Pergamon: New York, 1991; Vol. 5; Chapter 9.3.
- IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, 1997.
- FÜRSTNER, A. *Alkene Metathesis in Organic Synthesis*; Springer-Verlag: New York, 1998.
- VILLEMEN, D. *Tetrahedron Lett.* **1980**, 21, 1715–1718.
- TSUJI, J.; HASHIGUCHI, S. *Tetrahedron Lett.* **1980**, 21, 2955–2958.
- SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DiMARE, M.; O'REGAN, M. J. *Am. Chem. Soc.* **1990**, 112, 3875–3886.
- NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1992**, 114, 3974–3975.
- SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, 118, 100–110.
- SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. *Tetrahedron Lett.* **1999**, 40, 2247–2250.
- SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 953–956.
- GRUBBS, R. H.; MILLER, S. J.; FU, G. C. *Acc. Chem. Res.* **1995**, 28, 446–452.
- GRUBBS, R. H.; CHANG, S. *Tetrahedron* **1998**, 54, 4413–4450.
- TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, 34, 18–29.
- SCHMALZ, H.-G. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1833–1836.
- SCHUSTER, M.; BLECHERT, S. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2037–2056.
- ARMSTRONG, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.
- RANDALL, M. L.; SNAPPER, M. L. *J. Mol. Catal. A-Chem.* **1998**, 133, 29–40.
- PHILLIPS, A. J.; ABELL, A. D. *Aldrichimica Acta* **1999**, 32, 75–89.
- FÜRSTNER, A. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 3013–3043.
- ROY, R.; DAS, S. K. *Chem. Commun.* **2000**, 519–529.
- MAIER, M. E. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 2073–2077.
- HOVEYDA, A. H.; SCHROCK, R. R. *Chem. Eur. J.* **2001**, 7, 945–950.
- MULZER, J.; OHLER, E.; ENEV, V. S.; HANBAUER, M. *Adv. Synth. Catal.* **2002**, 344, 573–584.
- FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, 115, 3800–3801.
- CALLAM, C. S.; LOWARY, T. L. *Org. Lett.* **2000**, 2, 167–169.
- CRIMMINS, M. T.; KING, B. W. *J. Org. Chem.* **1996**, 61, 4192–4193.
- CRIMMINS, M. T.; KING, B. W.; ZUERCHER, W. J.; CHOY, A. L. *J. Org. Chem.* **2000**, 65, 8499–8509.
- CRIMMINS, M. T.; ZUERCHER, W. J. *Org. Lett.* **2000**, 2, 1065–1067.
- OVAA, H.; CODEE, J. D. C.; LASTDRAGER, B.; OVERKLEEF, H. S.; VAN DER MAREL, G. A.; VAN BOOM, J. H. *Tetrahedron Lett.* **1999**, 40, 5063–5066.
- HANESSIAN, S.; MARGARITA, R.; HALL, A.; JOHNSTONE, S.; TREMBLAY, M.; PARLANTI, L. *J. Am. Chem. Soc.* **2002**, 124, 13342–13343.
- SCHNEIDER, M. F.; JUNG, H.; BLECHERT, S. *Tetrahedron* **1995**, 51, 13003–13014.
- MEHTA, G.; UMARYE, J. D. *Org. Lett.* **2002**, 4, 1063–1066.
- FÜRSTNER, A.; KOCH, D.; LANGEMANN, K.; LEITNER, W.; SIX, C. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2466–2469.
- MARCO-CONTELLAS, J.; DE OPAZO, E. *J. Org. Chem.* **2000**, 65, 5416–5419.
- MARCO-CONTELLAS, J.; DE OPAZO, E. *J. Org. Chem.* **2002**, 67, 3705–3717.
- GHOSH, A. K.; CAPPIELLO, J.; SHIN, D. *Tetrahedron Lett.* **1998**, 39, 4651–4654.
- GHOSH, A. K.; LIU, C. *Chem. Commun.* **1999**, 1743–1744.
- GHOSH, A. K.; WANG, Y. J. *Am. Chem. Soc.* **2000**, 122, 11027–11028.
- GHOSH, A. K.; WANG, Y.; KIM, J. T. *J. Org. Chem.* **2001**, 66, 8973–8982.
- NELSON, S. G.; CHEUNG, W. S.; KASSICK, A. J.; HILFIKER, M. A. *J. Am. Chem. Soc.* **2002**, 124, 13654–13655.
- BORTEAU, J. G.; VAN DE WEGHE, P.;

- EUSTACHE, J. *Org. Lett.* **2001**, 3, 2737–2740.
- 42 REDDY, M. V. R.; REARICK, J. P.; HOCH, N.; RAMACHANDRAN, P. V. *Org. Lett.* **2001**, 3, 19–20.
- 43 RAMACHANDRAN, P. V.; CHANDRA, J. S.; REDDY, M. V. R. *J. Org. Chem.* **2002**, 67, 7547–7550.
- 44 DU, Y. M.; WIEMER, D. F. *Tetrahedron Lett.* **2001**, 42, 6069–6072.
- 45 HUANG, K.-S.; WANG, E.-C. *Tetrahedron Lett.* **2001**, 42, 6155–6157.
- 46 CHATTERJEE, A. K.; MORGAN, J. P.; SCHOLL, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, 122, 3783–3784.
- 47 ANDREANA, P. R.; MCLELLAN, J. S.; CHEN, Y.; WANG, P. G. *Org. Lett.* **2002**, 4, 3875–3878.
- 48 ARISAWA, M.; THEERALADANON, C.; NISHIDA, A.; NAKAGAWA, M. *Tetrahedron Lett.* **2001**, 42, 8029–8033.
- 49 OKADA, A.; OHSHIMA, T.; SHIBASAKI, M. *Tetrahedron Lett.* **2001**, 42, 8023–8027.
- 50 CONRAD, R. M.; GROGAN, M. J.; BERTOZZI, C. R. *Org. Lett.* **2002**, 4, 1359–1361.
- 51 NICOLAOU, K. C.; JENNINGS, M. P.; DAGNEAU, P. *Chem. Commun.* **2002**, 2480–2481.
- 52 BASIL, L. F.; NAKANO, H.; FRUTOS, R.; KOPACH, M.; MEYERS, A. I. *Synthesis* **2002**, 2064–2074.
- 53 NAKASHIMA, K.; INOUE, K.; SONO, M.; TORI, M. *J. Org. Chem.* **2002**, 67, 6034–6040.
- 54 MILLER, S. J.; KIM, S.-H.; CHEN, Z.-R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1995**, 117, 2108–2109.
- 55 FÜRSTNER, A.; LANGEMANN, K. *J. Org. Chem.* **1996**, 61, 8746–8749.
- 56 HOLT, D. J.; BARKER, W. D.; JENKINS, P. R.; DAVIES, D. L.; GARRATT, S.; FAWCETT, J.; RUSSELL, D. R.; GHOSH, S. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 3298–3300.
- 57 PAQUETTE, L. A.; SCHLOSS, J. D.; EFREMOV, I.; FABRIS, F.; GALLOU, F.; MENDEZ-ANDINO, J.; YANG, J. *Org. Lett.* **2000**, 2, 1259–1261.
- 58 BOYER, F. D.; HANNA, I.; NOLAN, S. P. *J. Org. Chem.* **2001**, 66, 4094–4096.
- 59 MENDEZ-ANDINO, J.; PAQUETTE, L. A. *Adv. Synth. Catal.* **2002**, 344, 303–311.
- 60 BOURGEOIS, D.; PANCRAZI, A.; RICARD, L.; PRUNET, J. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 726–728.
- 61 CODESIDO, M.; RODRIGUEZ, J. R.; CASTEDO, L.; GRANJA, J. R. *Org. Lett.* **2002**, 4, 1651–1654.
- 62 KRAFFT, M. E.; CHEUNG, Y. Y.; JULIANO-CAPUCAO, C. A. *Synthesis* **2000**, 1020–1026.
- 63 BUSZEK, K. R.; SATO, N.; JEONG, Y. *Tetrahedron Lett.* **2002**, 43, 181–184.
- 64 BABA, Y.; SAHA, G.; NAKAO, S.; IWATA, C.; TANAKA, T.; IBUKA, T.; OHISHI, H.; TAKEMOTO, Y. *J. Org. Chem.* **2001**, 66, 81–88.
- 65 NEVALAINEN, M.; KOSKINEN, A. M. P. *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 4060–4062.
- 66 NEVALAINEN, M.; KOSKINEN, A. M. P. *J. Org. Chem.* **2002**, 67, 1554–1560.
- 67 WALTERS, M. A.; LA, F.; DESHMUKH, P.; OMECINSKY, D. O. *J. Comb. Chem.* **2002**, 4, 125–130.
- 68 USHER, L. C.; ESTRELLA-JIMENEZ, M.; GHIVIRIGA, I.; WRIGHT, D. L. *Angew. Chem. Int. Ed. Engl.* **2002**, 41, 4560–4562.
- 69 LANGER, P.; ALBRECHT, U. *Synlett* **2002**, 1841–1842.
- 70 OESTERREICH, K.; KLEIN, I.; SPITZNER, D. *Synlett* **2002**, 1712–1714.
- 71 MOREHEAD, A.; GRUBBS, R. *Chem. Commun.* **1998**, 275–276.
- 72 RODRIGUEZ, J. R.; CASTEDO, L.; MASCARENAS, J. L. *Org. Lett.* **2000**, 2, 3209–3212.
- 73 RODRIGUEZ, J. R.; CASTEDO, L.; MASCARENAS, J. L. *Chem. Eur. J.* **2002**, 8, 2923–2930.
- 74 MASCARENAS, J. L.; RUMBO, A.; CASTEDO, L. *J. Org. Chem.* **1997**, 62, 8620–8621.
- 75 KIGOSHI, H.; SUZUKI, Y.; AOKI, K.; UEMURA, D. *Tetrahedron Lett.* **2000**, 41, 3927–3930.
- 76 TANG, H. F.; YUSUFF, N.; WOOD, J. L. *Org. Lett.* **2001**, 3, 1563–1566.
- 77 HANNA, I.; MICHAUT, V. *Org. Lett.* **2000**, 2, 1141–1143.
- 78 JOE, D.; OVERMAN, L. E. *Tetrahedron Lett.* **1997**, 38, 8635–8638.
- 79 DE ARMAS, P.; GARCIA-TELLADO, F.; MARRERO-TELLADO, J. J. *Eur. J. Org. Chem.* **2001**, 4423–4429.

- 80 WENZ, M.; GROSSBACH, D.; BEITZEL, M.; BLECHERT, S. *Synthesis* **1999**, 607–614.
- 81 KIM, S. H.; FUCHS, P. L. *Tetrahedron Lett.* **1996**, 37, 2545–2548.
- 82 KIM, S. H.; FIGUEROA, I.; FUCHS, P. L. *Tetrahedron Lett.* **1997**, 38, 2601–2604.
- 83 OJIMA, I.; LIN, S. N.; INOUE, T.; MILLER, M. L.; BORELLA, C. P.; GENG, X. D.; WALSH, J. J. *J. Am. Chem. Soc.* **2000**, 122, 5343–5353.
- 84 METAFERIA, B. B.; HOCH, J.; GLASS, T. E.; BANE, S. L.; CHATTERJEE, S. K.; SNYDER, J. P.; LAKDAWALA, A.; CORNETT, B.; KINGSTON, D. G. I. *Org. Lett.* **2001**, 3, 2461–2464.
- 85 MEHTA, G.; KUMARAN, S. *Chem. Commun.* **2002**, 1456–1457.
- 86 FORBES, M. D.; PATTON, J. T.; MYERS, T. L.; MAYNARD, H. D.; SMITH, D. W., JR.; SCHULZ, G. R.; WAGENER, K. B. *J. Am. Chem. Soc.* **1992**, 114, 10978–10980.
- 87 CHANG, S. B.; GRUBBS, R. H. *Tetrahedron Lett.* **1997**, 38, 4757–4760.
- 88 EVANS, P. A.; MURTHY, V. S. *J. Org. Chem.* **1998**, 63, 6768–6769.
- 89 TAYLOR, R. E.; ENGELHARDT, F. C.; YUAN, H. *Org. Lett.* **1999**, 1, 1257–1260.
- 90 GIERASCH, T. M.; CHYTIL, M.; DIDIUK, M. T.; PARK, J. Y.; URBAN, J. J.; NOLAN, S. P.; VERDINE, G. L. *Org. Lett.* **2000**, 2, 3999–4002.
- 91 POSTEMA, M. H. D.; PIPER, J. L. *Tetrahedron Lett.* **2002**, 43, 7095–7099.
- 92 BOITEAU, J. G.; VAN DE WEGHE, P.; EUSTACHE, J. *Tetrahedron Lett.* **2001**, 42, 239–242.
- 93 VAN DE WEGHE, P.; AOUN, D.; BOITEAU, J.-G.; EUSTACHE, J. *Org. Lett.* **2002**, 4, 4105–4108.
- 94 DENMARK, S. E.; YANG, S.-M. *J. Am. Chem. Soc.* **2002**, 124, 2102–2103.
- 95 HANSON, P. R.; STOIANOVA, D. S. *Tetrahedron Lett.* **1999**, 40, 3297–3300.
- 96 HANSON, P. R.; STOIANOVA, D. S. *Tetrahedron Lett.* **1998**, 39, 3939–3942.
- 97 STOIANOVA, D. S.; HANSON, P. R. *Org. Lett.* **2000**, 2, 1769–1772.
- 98 SPROTT, K. T.; HANSON, P. R. *J. Org. Chem.* **2000**, 65, 4721–4728.
- 99 SORENSEN, A. M.; NIELSEN, P. *Org. Lett.* **2000**, 2, 4217–4219.
- 100 SORENSEN, A. M.; NIELSEN, K. E.; VOGG, B.; JACOBSEN, J. P.; NIELSEN, P. *Tetrahedron* **2001**, 57, 10191–10201.
- 101 BORSTING, P.; SORENSEN, A. M.; NIELSEN, P. *Synthesis* **2002**, 797–801.
- 102 TREVITT, M.; GOUVERNEUR, V. *Tetrahedron Lett.* **1999**, 40, 7333–7336.
- 103 SCHUMAN, M.; TREVITT, M.; REDD, A.; GOUVERNEUR, V. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 2491–2493.
- 104 HANSON, P. R.; PROBST, D. A.; ROBINSON, R. E.; YAU, M. *Tetrahedron Lett.* **1999**, 40, 4761–4764.
- 105 WANNER, J.; HARNED, A. M.; PROBST, D. A.; POON, K. W. C.; KLEIN, T. A.; SNELGROVE, K. A.; HANSON, P. R. *Tetrahedron Lett.* **2002**, 43, 917–921.
- 106 BROWN, R. C. D.; CASTRO, J. L.; MORIGGI, J. D. *Tetrahedron Lett.* **2000**, 41, 3681–3685.
- 107 YAO, Q. W. *Org. Lett.* **2002**, 4, 427–430.
- 108 MOORE, J. D.; SPROTT, K. T.; HANSON, P. R. *Synlett* **2001**, 605–608.
- 109 SPAGNOL, G.; HECK, M. P.; NOLAN, S. P.; MIOSKOWSKI, C. *Org. Lett.* **2002**, 4, 1767–1770.
- 110 RENAUD, J.; OUELLET, S. G. *J. Am. Chem. Soc.* **1998**, 120, 7995–7996.
- 111 ASHE III, A. J.; FANG, X. D. *Org. Lett.* **2000**, 2, 2089–2091.
- 112 ASHE III, A. J.; YANG, H.; FANG, X.; KAMPF, J. W. *Organometallics* **2002**, 21, 4578–4580.
- 113 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, 114, 5426–5427.
- 114 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, 114, 7324–7325.
- 115 FU, G. C.; NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, 115, 9856–9857.
- 116 OVAA, H.; LEEUWENBURGH, M. A.; OVERKLEEF, H. S.; VAN DER MAREL, G. A.; VAN BOOM, J. H. *Tetrahedron Lett.* **1998**, 39, 3025–3028.
- 117 DELGADO, M.; MARTIN, J. D. *Tetrahedron Lett.* **1997**, 38, 6299–6300.
- 118 DELGADO, M.; MARTIN, J. D. *J. Org. Chem.* **1999**, 64, 4798–4816.
- 119 RUTJES, F.; KOOISTRA, T. M.; HIEMSTRA, H.; SCHOEMAKER, H. E. *Synlett* **1998**, 192–194.
- 120 EDWARDS, S. D.; LEWIS, T.; TAYLOR, R. J. K. *Tetrahedron Lett.* **1999**, 40, 4267–4270.

- 121 LINDERMAN, R. J.; SIEDLECKI, J.; ONEILL, S. A.; SUN, H. *J. Am. Chem. Soc.* **1997**, 119, 6919–6920.
- 122 DIRAT, O.; VIDAL, T.; LANGLOIS, Y. *Tetrahedron Lett.* **1999**, 40, 4801–4802.
- 123 CRIMMINS, M. T.; CHOY, A. L. *J. Am. Chem. Soc.* **1999**, 121, 5653–5660.
- 124 CRIMMINS, M. T.; TABET, E. A. *J. Am. Chem. Soc.* **2000**, 122, 5473–5476.
- 125 STEFINOVIC, M.; SNIECKUS, V. *J. Org. Chem.* **1998**, 63, 2808–2809.
- 126 CHANG, S.; GRUBBS, R. H. **1998**, 63, 864–866.
- 127 FUJIMURA, O.; FU, G. C.; GRUBBS, R. H. *J. Org. Chem.* **1994**, 59, 4029–4031.
- 128 CLARK, J. S.; KETTLE, J. G. *Tetrahedron Lett.* **1997**, 38, 123–126.
- 129 CLARK, J. S.; KETTLE, J. G. *Tetrahedron Lett.* **1997**, 38, 127–130.
- 130 STURINO, C. F.; WONG, J. C. Y. *Tetrahedron Lett.* **1998**, 39, 9623–9626.
- 131 WILLIAMS, D. R.; CORTEZ, G. S.; BOGEN, S. L.; ROJAS, C. M. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 4612–4615.
- 132 CLARK, J. S.; TREVITT, G. P.; BOYALL, D.; STAMMEN, B. *Chem. Commun.* **1998**, 2629–2630.
- 133 LEEUWENBURGH, M. A.; APPELDOORN, C. C. M.; VAN HOOFT, P. A. V.; OVERKLEEF, H. S.; VAN DER MAREL, G. A.; VAN BOOM, J. H. *Eur. J. Org. Chem.* **2000**, 873–877.
- 134 LIN, Y.-Y.; RISK, M.; RAY, S. M.; VAN ENGEN, D.; CLARDY, J.; GOLIK, J.; JAMES, J. C.; NAKANISHI, K. *J. Am. Chem. Soc.* **1981**, 103, 6773–6775.
- 135 YASUMOTO, T.; MURATA, M. *Chem. Rev.* **1993**, 93, 1897–1909.
- 136 OISHI, T.; NAGUMO, Y.; HIRAMA, M. *Chem. Commun.* **1998**, 1041–1042.
- 137 SASAKI, M.; NOGUCHI, T.; TACHIBANA, K. *Tetrahedron Lett.* **1999**, 40, 1337–1340.
- 138 MAEDA, K.; OISHI, T.; OGURI, H.; HIRAMA, M. *Chem. Commun.* **1999**, 1063–1064.
- 139 HIRAMA, M.; OISHI, T.; UEHARA, H.; INOUE, M.; MARUYAMA, M.; GURI, H.; SATAKE, M. *Science* **2001**, 294, 1904–1907.
- 140 KADOTA, I.; OHNO, A.; MATSUDA, K.; YAMAMOTO, Y. *J. Am. Chem. Soc.* **2001**, 123, 6702–6703.
- 141 KADOTA, I.; OHNO, A.; MATSUDA, K.; YAMAMOTO, Y. *J. Am. Chem. Soc.* **2002**, 124, 3562–3566.
- 142 GRIGG, R.; SRIDHARAN, V.; YORK, M. *Tetrahedron Lett.* **1998**, 39, 4139–4142.
- 143 MARTIN, R.; ALCON, M.; PERICAS, M. A.; RIERA, A. *J. Org. Chem.* **2002**, 67, 6896–6901.
- 144 FELPIN, F. X.; GIRARD, S.; VO-THANH, G.; ROBINS, R. J.; VILLIERAS, J.; LEBRETON, J. *J. Org. Chem.* **2001**, 66, 6305–6312.
- 145 HUNT, J. C. A.; LAURENT, P.; MOODY, C. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2378–2389.
- 146 KULANTHAIVEL, P.; HALLOCK, Y. F.; BOROS, C.; HAMILTON, S. M.; JANZEN, W. P.; BALLAS, L. M.; LOOMIS, C. R.; JIANG, J. B. *J. Am. Chem. Soc.* **1993**, 115, 6452–6453.
- 147 COOK, G. R.; SHANKER, P. S.; PETERSON, S. L. *Org. Lett.* **1999**, 1, 615–617.
- 148 FÜRSTNER, A.; THIEL, O. R. *J. Org. Chem.* **2000**, 65, 1738–1742.
- 149 WHITE, J. D.; HRNCIAR, P.; YOKOCHI, A. F. T. *J. Am. Chem. Soc.* **1998**, 120, 7359–7360.
- 150 BIRMAN, V. B.; RAWAL, V. H. *J. Org. Chem.* **1998**, 63, 9146–9147.
- 151 GONZALEZ-PEREZ, P.; PEREZ-SERRANO, L.; CASARRUBIOS, L.; DOMINGUEZ, G.; PEREZ-CASTELLS, J. *Tetrahedron Lett.* **2002**, 43, 4765–4767.
- 152 OVERKLEEF, H. S.; PANDIT, U. K. *Tetrahedron Lett.* **1996**, 37, 547–550.
- 153 BARRETT, A. G. M.; BAUGH, S. P. D.; GIBSON, V. C.; GILES, M. R. M., E. L.; PROCOPIOU, P. A. *Chem. Commun.* **1996**, 2231–2232.
- 154 BARRETT, A. G. M.; BAUGH, S. P. D.; GIBSON, V. C.; GILES, M. R.; MARSHALL, E. L.; PROCOPIOU, P. A. *Chem. Commun.* **1997**, 155–156.
- 155 BARRETT, A. G. M.; BAUGH, S. P. D.; BRADDOCK, D. C.; FLACK, K.; GIBSON, V. C.; GILES, M. R.; MARSHALL, E. L.; PROCOPIOU, P. A.; WHITE, A. J. P.; WILLIAMS, D. J. *J. Org. Chem.* **1998**, 63, 7893–7907.
- 156 BARRETT, A. G. M.; AHMED, M.; BAKER, S. P.; BAUGH, S. P. D.; BRADDOCK, D. C.; PROCOPIOU, P. A.; WHITE, A. J. P.; WILLIAMS, D. J. *J. Org. Chem.* **2000**, 65, 3716–3721.

- 157 DU, Y. M.; WIEMER, D. F. *J. Org. Chem.* **2002**, 67, 5701–5708.
- 158 BEAL, L. M.; MOELLER, K. D. *Tetrahedron Lett.* **1998**, 39, 4639–4642.
- 159 VO-THANH, G.; BOUCARD, V.; SAURIAT-DORIZON, H.; GUIBE, F. *Synlett* **2001**, 37–40.
- 160 BIERAUGEL, H.; JANSEN, T. P.; SCHOEMAKER, H. E.; HIEMSTRA, H.; VAN MAARSEVEEN, J. H. *Org. Lett.* **2002**, 4, 2673–2674.
- 161 MILLER, S. J.; BLACKWELL, H. E.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1995**, 117, 5855–5856.
- 162 MILLER, S. J.; BLACKWELL, H. E.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1996**, 118, 9606–9614.
- 163 RUTJES, F. P. J. T.; SCHOEMAKER, H. E. *Tetrahedron Lett.* **1997**, 38, 677–680.
- 164 HAMMER, K.; UNDHEIM, K. *Tetrahedron* **1997**, 53, 2309–2322.
- 165 HAMMER, K.; UNDHEIM, K. *Tetrahedron* **1997**, 53, 5925–5936.
- 166 ABELL, A. D.; GARDINER, J. *Org. Lett.* **2002**, 4, 3663–3666.
- 167 KOTHA, S.; SREENIVASACHARY, N.; MOHANRAJA, K.; DURANI, S. *Bioorg. Med. Chem. Lett.* **2001**, 11, 1421–1423.
- 168 HOFFMANN, T.; GMEINER, P. *Synlett* **2002**, 1014–1016.
- 169 CREIGHTON, C. J.; REITZ, A. B. *Org. Lett.* **2001**, 3, 893–895.
- 170 BLACKWELL, H. E.; GRUBBS, R. H. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 3281–3284.
- 171 BLACKWELL, H. E.; SADOWSKY, J. D.; HOWARD, R. J.; SAMPSON, J. N.; CHAO, J. A.; STEINMETZ, W. E.; O'LEARY, D. J.; GRUBBS, R. H. *J. Org. Chem.* **2001**, 66, 5291–5302.
- 172 REICHWEIN, J. F.; LISKAMP, R. M. J. *Eur. J. Org. Chem.* **2000**, 2335–2344.
- 173 REICHWEIN, J. F.; VERSLUIS, C.; LISKAMP, R. M. J. *J. Org. Chem.* **2000**, 65, 6187–6195.
- 174 REICHWEIN, J. F.; WELS, B.; KRUIJTZER, J. A. W.; VERSLUIS, C.; LISKAMP, R. M. J. *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 3684–3687.
- 175 REICHWEIN, J. F.; LISKAMP, R. M. J. *Tetrahedron Lett.* **1998**, 39, 1243–1246.
- 176 KAZMAIER, U.; MAIER, S. *Org. Lett.* **1999**, 1, 1763–1766.
- 177 RIPKA, A. S.; BOHACEK, R. S.; RICH, D. H. *Bioorg. Med. Chem. Lett.* **1998**, 8, 357–360.
- 178 FINK, B. E.; KYM, P. R.; KATZEN-ELLENBOGEN, J. A. *J. Am. Chem. Soc.* **1998**, 120, 4334–4344.
- 179 BIJANI, C.; VARRAY, S.; LAZARO, R.; MARTINEZ, J.; LAMATY, F.; KIEFFER, N. *Tetrahedron Lett.* **2002**, 43, 3765–3767.
- 180 PRABHAKARAN, E. N.; RAO, I. N.; BORUAH, A.; IQBAL, J. *J. Org. Chem.* **2002**, 67, 8247–8250.
- 181 CLARK, T. D.; GHADIRI, M. R. *J. Am. Chem. Soc.* **1995**, 117, 12364–12365.
- 182 PISCOPIO, A. D.; MILLER, J. F.; KOCH, K. *Tetrahedron Lett.* **1997**, 38, 7143–7146.
- 183 PISCOPIO, A. D.; MILLER, J. F.; KOCH, K. *Tetrahedron Lett.* **1998**, 39, 2667–2670.
- 184 PISCOPIO, A. D.; MILLER, J. F.; KOCH, K. *Tetrahedron* **1999**, 55, 8189–8198.
- 185 CONDE-FRIEBOES, K.; ANDERSEN, S.; BREINHOIT, J. *Tetrahedron Lett.* **2000**, 41, 9153–9156.
- 186 JARVO, E. R.; COPELAND, G. T.; PAPAIOANNOU, N.; BONITATEBUS, P. J.; MILLER, S. J. *J. Am. Chem. Soc.* **1999**, 121, 11638–11643.
- 187 PERNERSTORFER, J.; SCHUSTER, M.; BLECHERT, S. *Chem. Commun.* **1997**, 1949–1950.
- 188 SCHMIEDEBERG, N.; KESSLER, H. *Org. Lett.* **2002**, 4, 59–62.
- 189 MCKERVEY, M. A.; PITARCH, M. C. C. *Chem. Commun.* **1996**, 1689–1690.
- 190 LECOURT, T.; MALLET, J. M.; SINAY, P. *Tetrahedron Lett.* **2002**, 43, 5533–5536.
- 191 ARAKAWA, K.; EGUCHI, T.; KAKINUMA, K. *J. Org. Chem.* **1998**, 63, 4741–4745.
- 192 LUNING, U.; FAHRENKRUG, F.; HAGEN, M. *Eur. J. Org. Chem.* **2001**, 2161–2163.
- 193 CHEN, G. W.; KIRSCHNING, A. *Chem. Eur. J.* **2002**, 8, 2717–2729.
- 194 IBRAHIM, Y. A.; BEHBEHANI, H.; IBRAHIM, M. R.; ABRAR, N. M. *Tetrahedron Lett.* **2002**, 43, 6971–6974.
- 195 IBRAHIM, Y. A.; BEHBEHANI, H.; IBRAHIM, M. R. *Tetrahedron Lett.* **2002**, 43, 4207–4210.
- 196 FÜRSTNER, A.; LANGEMANN, K. *J. Org. Chem.* **1996**, 61, 3942–3943.
- 197 FÜRSTNER, A.; KINDLER, N. *Tetrahedron Lett.* **1996**, 37, 7005–7008.

- 198 LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **2000**, 2, 2145–2147.
- 199 WU, Y. S.; ESSER, L.; DE BRABANDER, J. K. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 4308–4310.
- 200 FEUTRILL, J. T.; HOLLOWAY, G. A.; HILLI, F.; HUGEL, H. M.; RIZZACASA, M. A. *Tetrahedron Lett.* **2000**, 41, 8569–8572.
- 201 FÜRSTNER, A.; DIERKES, T.; THIEL, O. R.; BLANDA, G. *Chem. Eur. J.* **2001**, 7, 5286–5298.
- 202 CHRISTOFFERS, J.; OERTLING, H.; FISCHER, P.; FREY, W. *Synlett* **2002**, 957–961.
- 203 BANWELL, M. G.; MCRAE, K. J. *Org. Lett.* **2000**, 2, 3583–3586.
- 204 FÜRSTNER, A.; THIEL, O. R.; ACKERMANN, L. *Org. Lett.* **2001**, 3, 449–451.
- 205 HOURI, A. F.; XU, Z.; COGAN, D. A.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1995**, 117, 2943–2944.
- 206 XU, Z.; JOHANNES, C. W.; SALMAN, S. S.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1996**, 118, 10926–10927.
- 207 BALTRUSCH, A. W.; BRACHER, F. *Synlett* **2002**, 1724–1726.
- 208 ARISAWA, M.; KANEKO, H.; NISHIDA, A.; YAMAGUCHI, K.; NAKAGAWA, M. *Synlett* **2000**, 841–843.
- 209 ARISAWA, M.; KANEKO, H.; NISHIDA, A.; NAKAGAWA, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 959–964.
- 210 CABREJAS, L. M. M.; ROHRBACH, S.; WAGNER, D.; KALLEN, J.; ZENKE, G.; WAGNER, J. *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 2443–2446.
- 211 WAGNER, J.; CABREJAS, L. M. M.; GROSSMITH, C. E.; PAPAGEORGIOU, C.; SENIA, F.; WAGNER, D.; FRANCE, J.; NOLAN, S. P. *J. Org. Chem.* **2000**, 65, 9255–9260.
- 212 DVORAK, C. A.; SCHMITZ, W. D.; POON, D. J.; PRYDE, D. C.; LAWSON, J. P.; AMOS, R. A.; MEYERS, A. I. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 1664–1666.
- 213 PAQUETTE, L. A.; TAE, J. S.; ARRINGTON, M. P.; SADOUN, A. H. *J. Am. Chem. Soc.* **2000**, 122, 2742–2748.
- 214 GARBACCIO, R. M.; DANISHEFSKY, S. J. *Org. Lett.* **2000**, 2, 3127–3129.
- 215 GARBACCIO, R. M.; STACHEL, S. J.; BAESCHLIN, D. K.; DANISHEFSKY, S. J. *J. Am. Chem. Soc.* **2001**, 123, 10903–10908.
- 216 BACH, T.; LEMARCHAND, A. *Synlett* **2002**, 1302–1304.
- 217 PALEY, R. S.; ESTROFF, L. A.; GAUGUET, J. M.; HUNT, D. K.; NEWLIN, R. C. *Org. Lett.* **2000**, 2, 365–368.
- 218 PAQUETTE, L. A.; BASU, K.; EPPICH, J. C.; HOFFERBERTH, J. E. *Helv. Chim. Acta* **2002**, 85, 3033–3051.
- 219 MORTREUX, A.; BLANCHARD, M. J. *J. Chem. Soc., Chem. Commun.* **1974**, 786–787.
- 220 BENCHEIK, A.; PETIT, M.; MORTREUX, A.; PETIT, F. *J. Mol. Catal.* **1982**, 15, 93–101.
- 221 MORTREUX, A.; DELGRANGE, J. C.; BLANCHARD, M.; LUBOCHINSKY, B. *J. Mol. Catal.* **1977**, 2, 73–82.
- 222 BUNZ, U. H. F.; KLOPPENBURG, L. *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 478–481.
- 223 KROUSE, S. A.; SCHROCK, R. R. *Macromolecules* **1989**, 22, 2569–2576.
- 224 ZHANG, X.-P.; BAZAN, G. C. *Macromolecules* **1994**, 27, 4627–4628.
- 225 PSCHIRER, N. G.; VAUGHN, M. E.; DONG, Y. B.; ZUR LOYE, H.-C.; BUNZ, U. H. F. *Chem. Commun.* **2000**, 85–86.
- 226 KANETA, N.; HIRAI, T.; MORI, M. *Chem. Lett.* **1995**, 627–628.
- 227 KANEKA, N.; HIKICHI, K.; ASAKA, S. I. U., M.; MORI, M. *Chem. Lett.* **1995**, 1055–1056.
- 228 FÜRSTNER, A.; SEIDEL, G. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 1734–1736.
- 229 FÜRSTNER, A.; MATHES, C.; LEHMANN, C. W. *J. Am. Chem. Soc.* **1999**, 121, 9453–9454.
- 230 FÜRSTNER, A.; RUMBO, A. *J. Org. Chem.* **2000**, 65, 2608–2611.
- 231 FÜRSTNER, A.; MATHES, C.; LEHMANN, C. W. *Chem. Eur. J.* **2001**, 7, 5299–5317.
- 232 FÜRSTNER, A.; GUTH, O.; RUMBO, A.; SEIDEL, G. *J. Am. Chem. Soc.* **1999**, 121, 11108–11113.
- 233 FÜRSTNER, A.; RADKOWSKI, K.; GRABOWSKI, J.; WIRTZ, C.; MYNOTT, R. *J. Org. Chem.* **2000**, 65, 8758–8762.
- 234 FÜRSTNER, A.; GRELA, K. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 1234–1236.

- 235 KINOSHITA, A.; SAKAKIBARA, N.; MORI, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388–12389.
- 236 MORI, M.; SAKAKIBARA, N.; KINOSHITA, A. *J. Org. Chem.* **1998**, *63*, 6082–6083.
- 237 RENAUD, J.; GRAF, C. D.; OBERER, L. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3101–3104.
- 238 KINOSHITA, A.; MORI, M. *J. Org. Chem.* **1996**, *61*, 8356–8357.
- 239 KITAMURA, T.; SATO, Y.; MORI, M. *Adv. Synth. Catal.* **2002**, *344*, 678–693.
- 240 HAMMER, K.; UNDHEIM, K. *Tetrahedron* **1997**, *53*, 10603–10614.
- 241 EFSKIND, J.; ROMMING, C.; UNDHEIM, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697–2703.
- 242 HOVEN, G. B.; EFSKIND, J.; ROMMING, C.; UNDHEIM, K. *J. Org. Chem.* **2002**, *67*, 2459–2463.
- 243 HUANG, J.; XIONG, H.; HSUNG, R. P.; RAMESHKUMAR, C.; MULDER, J. A.; GREBE, T. P. *Org. Lett.* **2002**, *4*, 2417–2420.
- 244 KIM, S.-H.; BOWDEN, N.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801–10802.
- 245 KIM, S.-H.; ZUERCHER, W. J.; BOWDEN, N.; GRUBBS, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081.
- 246 ZUERCHER, W. J.; SCHOLL, M.; GRUBBS, R. H. *J. Org. Chem.* **1998**, *63*, 4291–4298.
- 247 BOYER, F. D.; HANNA, I.; RICARD, L. *Org. Lett.* **2001**, *3*, 3095–3098.
- 248 COATES, G. W.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 229–230.
- 249 BASSINDALE, M. J.; HAMLEY, P.; LEITNER, A.; HARRITY, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247–3250.
- 250 EDWARDS, A. S.; WYBROW, R. A. J.; JOHNSTONE, C.; ADAMS, H.; HARRITY, J. P. A. *Chem. Commun.* **2002**, 1542–1543.
- 251 CLARK, J. S.; HAMELIN, O. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 372–374.
- 252 ZUERCHER, W. J.; HASHIMOTO, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640.
- 253 HARRITY, J. P. A.; VISSER, M. S.; GLEASON, J. D.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488–1489.
- 254 HARRITY, J. P. A.; LA, D. S.; CEFALO, D. R.; VISSER, M. S.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343–2351.
- 255 JOHANNES, C. W.; VISSER, M. S.; WEATHERHEAD, G. S.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340–8347.
- 256 OSIPOV, S. N.; KOBELIKOVA, N. M.; SHCHETNIKOV, G. T.; KOLOMIETS, A. F.; BRUNEAU, C.; DIXNEUF, P. H. *Synlett* **2001**, 621–622.
- 257 OSIPOV, S. N.; ARTYUSHIN, O. I.; KOLOMIETS, A. F.; BRUNEAU, C.; PICQUET, M.; DIXNEUF, P. H. *Eur. J. Org. Chem.* **2001**, 3891–3897.
- 258 OVAA, H.; STAPPER, C.; VAN DER MAREL, G. A.; OVERKLEEF, H. S.; VAN BOOM, J. H.; BLECHERT, S. *Tetrahedron* **2002**, *58*, 7503–7518.
- 259 BUSCHMANN, N.; RUCKERT, A.; BLECHERT, S. *J. Org. Chem.* **2002**, *67*, 4325–4329.
- 260 STRAGIES, R.; BLECHERT, S. *Tetrahedron* **1999**, *55*, 8179–8188.
- 261 CHOI, T. L.; GRUBBS, R. H. *Chem. Commun.* **2001**, 2648–2649.
- 262 MINGER, T. L.; PHILLIPS, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357–5359.
- 263 MORI, M.; KUZUBA, Y.; KITAMURA, T.; SATO, Y. *Org. Lett.* **2002**, *4*, 3855–3858.
- 264 BENTZ, D.; LASCHAT, S. *Synthesis* **2000**, 1766–1773.
- 265 ALEXAKIS, A.; CROSET, K. *Org. Lett.* **2002**, *4*, 4147–4149.
- 266 SUTTON, A. E.; SEIGAL, B. A.; FINNEGAN, D. F.; SNAPPER, M. L. *J. Am. Chem. Soc.* **2002**, 13390–13391.
- 267 HUWE, C. M.; VELDER, J.; BLECHERT, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2376–2378.
- 268 HUWE, C. M.; BLECHERT, S. *Synthesis* **1997**, 61–67.
- 269 WALLACE, D. J.; COWDEN, C. J.; KENNEDY, D. J.; ASHWOOD, M. S.; COTTRELL, I. F.; DOLLING, U. H. *Tetrahedron Lett.* **2000**, *41*, 2027–2029.
- 270 WALLACE, D. J.; BULGER, P. G.; KENNEDY, D. J.; ASHWOOD, M. S.; COTTRELL, I. F.; DOLLING, U. H. *Synlett* **2001**, 357–360.
- 271 LAUTENS, M.; HUGHES, G. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 129–131.

- 272 MARSELLA, M. J.; MAYNARD, H. D.; GRUBBS, R. H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1101–1103.
- 273 DIJKSTRA, H. P.; CHUCHURYUKIN, A.; SUIJKERBUIJK, B.; VAN KLINK, G. P. M.; MILLS, A. M.; SPEK, A. L.; VAN KOTEN, G. *Adv. Synth. Catal.* **2002**, *344*, 771–780.
- 274 RUWWE, J.; MARTIN-ALVAREZ, J. M.; HORN, C. R.; BAUER, E. B.; SZAFERT, S.; LIS, T.; HAMPEL, D.; CAGLE, P. C.; GLADYSZ, J. A. *Chem. Eur. J.* **2001**, *7*, 3931–3950.
- 275 DIETRICH-BUCHECKER, C.; RAPENNE, G.; SAUVAGE, J.-P. *Coord. Chem. Rev.* **1999**, *186*, 167–176.
- 276 MOHR, B.; WECK, M.; SAUVAGE, J.-P.; GRUBBS, R. H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1308–1310.
- 277 RAPENNE, G.; DIETRICH-BUCHECKER, C.; SAUVAGE, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 994–1001.
- 278 WECK, M.; MOHR, B.; SAUVAGE, J.-P.; GRUBBS, R. H. *J. Org. Chem.* **1999**, *64*, 5463–5471.
- 279 HAMILTON, D. G.; FEEDER, N.; TEAT, S. J.; SANDERS, J. K. M. *New J. Chem.* **1998**, *22*, 1019–1021.
- 280 KIDD, T. J.; LEIGH, D. A.; WILSON, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600.
- 281 LEIGH, D. A.; LUSBY, P. J.; TEAT, S. J.; WILSON, A. J.; WONG, J. K. Y. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1538–1543.
- 282 ANDRIEVSKY, A.; AHUIS, F.; SESSLER, J. L.; VÖGTLE, F.; GUDAT, D.; MOINI, M. *J. Am. Chem. Soc.* **1998**, *120*, 9712–9713.
- 283 WISNER, J. A.; BEER, P. D.; GREW, M. G. B.; SAMBROOK, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 12469–12476.
- 284 DIETRICH-BUCHECKER, C.; RAPENNE, G. N.; SAUVAGE, J.-P. *Chem. Commun.* **1997**, 2053–2054.
- 285 DIETRICH-BUCHECKER, C.; SAUVAGE, J.-P. *Chem. Commun.* **1999**, 615–616.
- 286 COLLIN, J. P.; LAEMMEL, A. C.; SAUVAGE, J.-P. *New J. Chem.* **2001**, *25*, 22–24.
- 287 ROWAN, S. J.; CANTRILL, S. J.; COUSINS, G. R. L.; SANDERS, J. K. M.; STODDART, J. F. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 898–952.
- 288 LEHN, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463.
- 289 CARDULLO, F.; CALAMA, M. C.; SNELLINK-RUEL, B. H. M.; WEIDMANN, J. L.; BIELEJEWSKA, A.; FOKKENS, R.; NIBBERING, N. M. M.; TIMMERMAN, P.; REINHOUTD, D. N. *Chem. Commun.* **2000**, 367–368.
- 290 PRINS, L. J.; VERHAGE, J. J.; DE JONG, F.; TIMMERMAN, P.; REINHOUTD, D. N. *Chem. Eur. J.* **2002**, *8*, 2302–2313.
- 291 WENDLAND, M. S.; ZIMMERMAN, S. C. *J. Am. Chem. Soc.* **1999**, *121*, 1389–1390.
- 292 SCHULTZ, L. G.; ZHAO, Y.; ZIMMERMAN, S. C. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1962–1966.
- 293 ZIMMERMAN, S. C.; WENDLAND, M. S.; RAKOW, N. A.; ZHAROV, I.; SUSLICK, K. S. *Nature* **2002**, *418*, 399–403.
- 294 SMITH III, A. B.; KOZMIN, S. A.; ADAMS, C. M.; PAONE, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984–4985.
- 295 SMITH III, A. B.; ADAMS, C. M.; KOZMIN, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990–991.
- 296 PAQUETTE, L. A.; FABRIS, F.; TAE, J. S.; GALLUCCI, J. C.; HOFFERBERTH, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391–3398.
- 297 LEE, D.; SELLO, J. K.; SCHREIBER, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648–10649.
- 298 FÜRSTNER, A.; MULLER, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814–7821.
- 299 GEORG, G. I.; AHN, Y. M.; BLACKMAN, B.; FAROKHI, F.; FLAHERTY, P. T.; MOSSMAN, C. J.; ROY, S.; YANG, K. L. *Chem. Commun.* **2001**, 255–256.
- 300 HOFLE, G.; BEDORF, N.; STEINMETZ, H.; SCHOMBURG, D.; GERTH, K.; REICHENBACH, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567–1569.
- 301 NICOLAOU, K. C.; HE, Y.; VOURLOUMIS, D.; VALLBERG, H.; YANG, Z. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2399–2401.
- 302 NICOLAOU, K. C.; HE, Y.; VOURLOUMIS, D.; VALLBERG, H.; ROSCHANGAR, F.; SARABIA, F.; NINKOVIC, S.; YANG, Z.; TRUJILLO, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973.
- 303 YANG, Z.; HE, Y.; VOURLOUMIS, D.; VALLBERG, H.; NICOLAOU, K. C. *Angew.*

- Chem. Int. Ed. Engl.* **1997**, *36*, 166–168.
- 304** NICOLAOU, K. C.; HE, Y.; ROSCHANGAR, F.; KING, N. P.; VOURLOUMIS, D.; LI, T. H. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 84–87.
- 305** SCHINZER, D.; LIMBERG, A.; BAUER, A.; BOHM, O. M.; CORDES, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523–524.
- 306** MENG, D.; SU, D.-S.; BALOG, A.; BERTINATO, P.; SORENSEN, E. J.; DANISHEFSKY, S. J.; ZHENG, Y.-H.; CHOU, T.-C.; HE, L.; HORWITZ, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.
- 307** MENG, D. F.; BERTINATO, P.; BALOG, A.; SU, D. S.; KAMENECKA, T.; SORENSEN, E. J.; DANISHEFSKY, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.
- 308** BISWAS, K.; LIN, H.; NJARDARSON, J. T.; CHAPPELL, M. D.; CHOU, T. C.; GUAN, Y. B.; TONG, W. P.; HE, L. F.; HORWITZ, S. B.; DANISHEFSKY, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825–9832.
- 309** RIVKIN, A.; BISWAS, K.; CHOU, T.-C.; DANISHEFSKY, S. J. *Org. Lett.* **2002**, *4*, 4081–4084.
- 310** NICOLAOU, K. C.; WINSSINGER, N.; PASTOR, J.; NINKOVIC, S.; SARABIA, F.; HE, Y.; VOURLOUMIS, D.; YANG, Z.; LI, T.; GIANNAKAKOU, P.; HAMEL, E. *Nature* **1997**, *387*, 268–272.
- 311** MARTIN, S. F.; LIAO, Y.; WONG, Y.; REIN, T. *Tetrahedron Lett.* **1994**, *35*, 691–694.
- 312** MARTIN, S. F.; HUMPHREY, J. M.; ALI, A.; HILLIER, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866–867.
- 313** HUMPHREY, J. M.; LIAO, Y. S.; ALI, A.; REIN, T.; WONG, Y. L.; CHEN, H. J.; COURTNEY, A. K.; MARTIN, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584–8592.

2.3

Catalytic Asymmetric Olefin Metathesis

Amir H. Hoveyda

2.3.1

Introduction

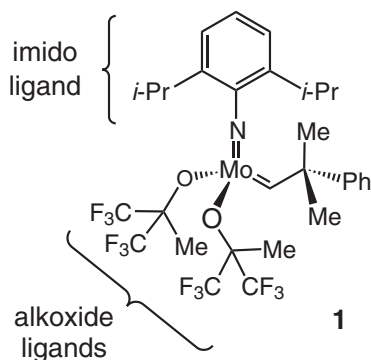
Rarely has a class of transformations so strongly influenced the field of organic synthesis as catalytic olefin metathesis has in the past decade [1]. Whether it is in the context of development of new methods or as part of total synthesis of a complex molecule, these catalytic reactions have been utilized to prepare a wide range of compounds, including small, medium, and large rings [2]. Only a few years ago, an alkene metathesis step was viewed as a daring application of a relatively unknown technology in a multi-step synthesis. Today, metathesis-based approaches are employed with such regularity that their use is considered somewhat routine.

With regard to the synthesis of optically pure materials, however, catalytic olefin metathesis has largely served a supporting role. In cases where ring-closing metathesis (RCM) is called for, an already optically pure diene is treated with an achiral metal catalyst to deliver a non-racemic cyclic unsaturated product [2a–c, 2e,f,h]. Alternatively, a racemic product obtained by metathesis may be catalytically resolved [2b]. Optically enriched cyclic alkenes are similarly employed in instances where ring-opening metathesis (ROM) is needed [2d,g]. Although such strategies have led to a number of notable and impressive accomplishments in asymmetric synthesis, some of the unique attributes of catalytic olefin metathesis can be realized only if chiral optically pure catalysts for olefin metathesis are available. This claim is connected to the fact that one of the most useful characteristics of metathetic processes is their ability to promote efficient skeletal rearrangements: simple achiral or racemic substrates may be transformed into complex non-racemic organic molecules. In numerous instances, products that are rendered readily available by a chiral metathesis catalyst would be accessible, and often less selectively, only by a longer route if alternative synthetic methods were to be used.

2.3.2

The Catalyst Construct

The makeup of Mo-based complexes, represented by **1** [3], offers the most attractive opportunity for the design, synthesis, and development of effective chiral metathesis catalysts. This idea is based on several factors: (1) Mo-based complexes such as **1** possess a modular structure involving imido and alkoxide moieties that do not disassociate from the metal center in the course of the catalytic cycle [4]. Any structural alteration of these ligands could lead to a notable effect on the reaction outcome and may be employed to control both selectivity and reactivity. (2) Alkoxide moieties offer an excellent opportunity for incorporation of chirality within the catalyst structure through installment of non-racemic chiral bis(hydroxy) ligands. (3) Mo-based complexes provide appreciable levels of activity and may be utilized to prepare highly substituted olefins.

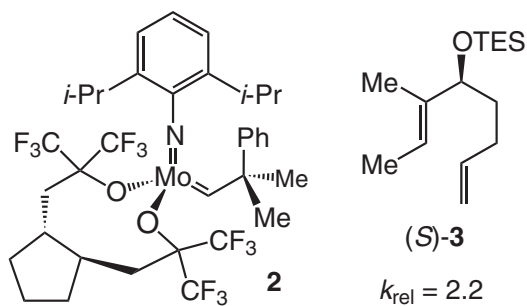


With the above considerations in mind, during the past 5 years our group, in collaboration with the research team of Schrock at MIT, has prepared and examined numerous chiral Mo-based catalysts for both asymmetric RCM (ARCM) and asymmetric ROM (AROM) transformations [5]. In this article, we highlight several efficient and enantioselective reactions that are catalyzed by these chiral Mo complexes [6]. The structural modularity inherent to the Mo-based systems allows screening of catalyst pools, so that optimal reactivity and selectivity levels are identified expeditiously. Recent advances towards the development of chiral Ru-based metathesis catalysts will also be discussed.

2.3.3

Mo-Catalyzed Kinetic Resolution With Hexafluoro-Mo Catalysts [7]

The preparation and catalytic activity of chiral complex **2**, based on the original Mo-alkylidene **1**, was disclosed by Grubbs and Fujimura [8]. These workers report on the kinetic resolution of various dienes [9]. As the case regarding the resolution of **3** indicates, however, levels of enantiodifferentiation were typically low ($k_{\text{rel}} < 3$).



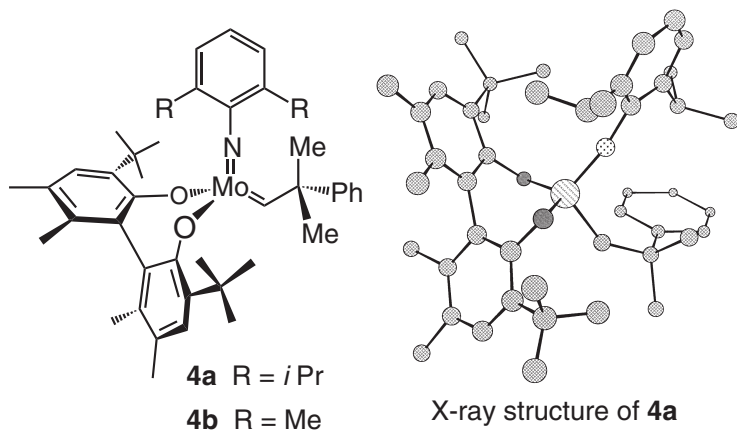
2.3.4

Chiral Mo-Diolate Complexes for Kinetic Resolution and Asymmetric Synthesis

2.3.4.1

Chiral Biphen-Mo Catalysts

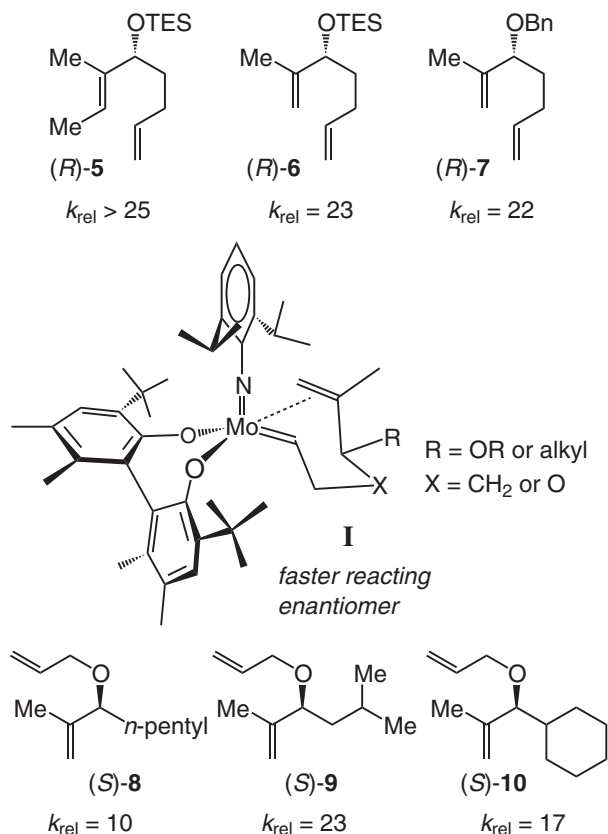
To examine the possibility of a more selective catalytic olefin metathesis, we first prepared chiral Mo-based complexes **4a** and **4b** [10]. This approach was not without precedence: related chiral Mo complexes were initially synthesized in 1993 by Schrock and coworkers to promote polymer synthesis [6]. We judged that these biphen-based systems would initiate olefin metathesis with high asymmetric induction due to their rigidity and the steric differentiation imposed on the chiral complex's binding pocket. Mo complexes **4a** and **4b** are orange solids that are indefinitely stable when kept under an inert atmosphere.



2.3.4.2

Catalytic Kinetic Resolution Through Mo-Catalyzed ARCM

The catalytic kinetic resolution of various dienes through ARCM can be carried out efficiently at 22 °C in the presence of 5 mol% **4a** [10]. As the data in Scheme 2.3-1



Scheme 2.3-1. Mo-catalyzed kinetic resolution of 1,6-dienes through ARCM.

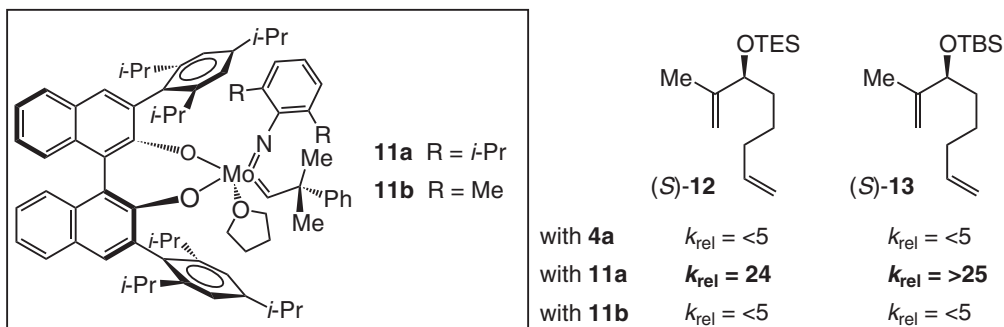
illustrate, 1,6-dienes 5–7 are resolved with excellent enantiocontrol ($k_{\text{rel}} > 20$) [11]. Chiral catalyst **4a** promotes the resolution of allylic ethers 8–10 as well [12].

The higher levels of enantioselectivity attained through the use of **4a** (vs. **2**) is likely due to a strong preference for ARCM reactions to proceed via Mo alkylidenes such as **I** (Scheme 2.3-1). The intermediacy (higher reactivity) of the *anti* Mo alkylidene (alkylidene C–C *anti* to Mo=N) is based on extensive mechanistic studies [13]. The stereochemistry of olefin-transition metal association is consistent with the position of the Mo-centered LUMO of the chiral complex [13b, 14]. The 1,1-disubstituted olefin interacts with Mo away from the protruding *t*-Bu group of the diolate and *i*-Pr groups of the imido ligands (see X-ray structure of **4a**).

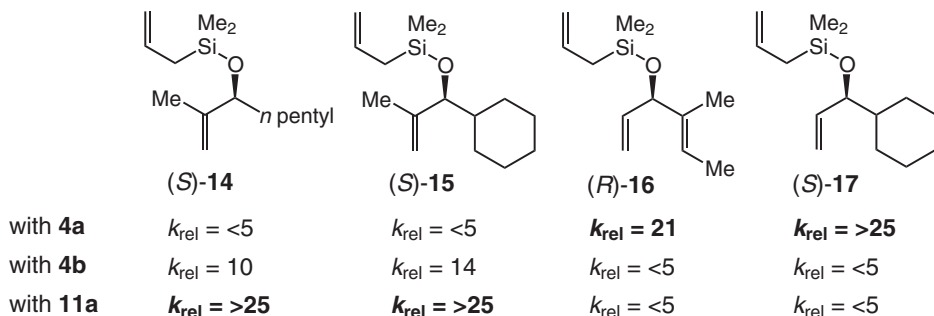
2.3.4.3

Catalyst Modularity and Optimization of Mo-Catalyzed ARCM Efficiency and Selectivity

Despite the high asymmetric induction observed in the Mo-catalyzed ARCM of 1,6-dienes, when **4a** and **4b** are used in reactions involving 1,7-dienes, inferior asym-



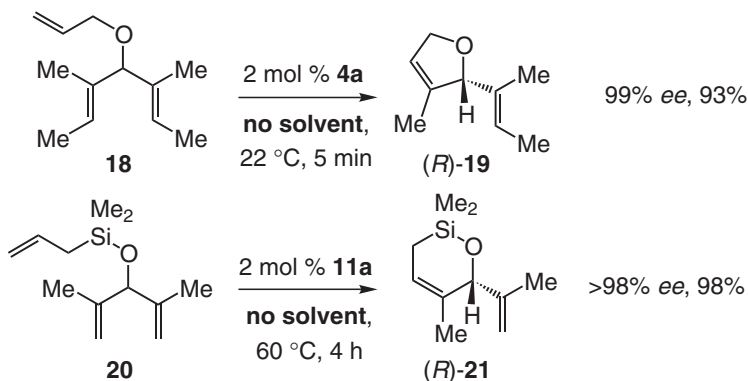
Scheme 2.3-2. Mo-catalyzed kinetic resolution of 1,7-dienes and the importance of subtle structural modification of the chiral catalysts.



Scheme 2.3-3. Small structural changes within the substrate structure can alter the identity of the optimum chiral metathesis catalyst.

metric induction is obtained. For example, as illustrated in Scheme 2.3-2, dienes **12** and **13** are not resolved with useful selectivity ($k_{\text{rel}} < 5$) when **4a** is employed as the catalyst. To address this shortcoming, we took advantage of the modular character of the Mo complexes and prepared a range of chiral complexes as potentially effective catalysts. Accordingly, as depicted in Scheme 2.3-2, we discovered that binol-based complex **11a** promotes the RCM of dienes **12** and **13** with outstanding levels of selectivity ($k_{\text{rel}} = 24$ and >25 , respectively) [15]. Binol-based complex **11b**, bearing the (dimethyl)phenylimido ligand (vs. (di(*iso*)-propyl)phenylimido of **11a**), is not an efficient catalyst for the kinetic resolution of the dienes **12** and **13**.

The data in Scheme 2.3-3 illustrate that various 1,7-dienes can be resolved with excellent levels of selectivity and efficiency. These findings provide further evidence regarding the importance of the availability of a diverse set of chiral catalysts. Although binol-based complexes (e.g., **11a**) typically promote ARCM of 1,7-dienes with higher selectivity than the biphen-based catalysts (e.g., **4a**), such a generalization is not always true. As expected, **11a** catalyzes the kinetic resolution of 1,7-dienes **14** and **15** with $k_{\text{rel}} > 25$. Unlike biphen complex **4a**, however, the closely related **4b** also provides appreciable enantioselection, albeit less effectively than



Scheme 2.3-4. Mo-catalyzed ARCM of achiral trienes can be effected efficiently, enantioselectively and in the absence of solvent.

11a. With substrates **16** and **17**, where two terminal alkenes are involved, the selectivity trend is reversed: now, the biphen-based complex **4a** is the only efficient catalyst. Although each catalyst is not optimal in every instance, efficient resolution of a wide range of chiral oxygenated 1,6- and 1,7-dienes can be achieved by different chiral Mo complexes.

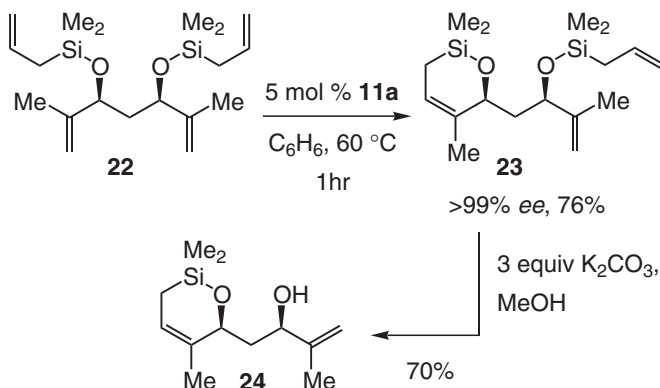
2.3.4.4

Catalytic Asymmetric Synthesis Through Mo-Catalyzed ARCM

The arena in which catalytic asymmetric olefin metathesis can have the largest impact on organic synthesis is the desymmetrization of readily accessible achiral molecules. Two examples are illustrated in Scheme 2.3-4. Treatment of achiral triene **18** with 5 mol % **4a** leads to the formation of (*R*)-**19** in 99% *ee* and 93% yield [12]. The reaction is complete within 5 min at 22 °C and, importantly, does not require a solvent. Another example is illustrated in Scheme 2.3-4. Here, binol complex **11a** is used to promote the formation of optically pure (*R*)-**21** from siloxy triene **20** in nearly quantitative yield. Once again, no solvents are needed [15]. Readily accessible substrates are rapidly transformed to optically enriched molecules that are otherwise significantly more difficult to access without generating solvent waste.

In connection with reactions where a solvent is required, it must be noted that all transformations promoted by chiral Mo catalysts can be carried out in toluene (in addition to benzene) or alkanes (e.g., *n*-pentane) with equal efficiency (see below for specific examples). Moreover, although 5 mol % catalyst is typically used, 1–2 mol % loading often delivers equally efficient and selective transformations.

As the above studies predicate, reaction of **18** is significantly less efficient with **11a** (<5% conv in 18 h) and that of **20** proceeds only to 50% conversion in 24 hours in the presence of **4a** (65% *ee*). Remarkably, in the latter transformation, even in a 0.1 M solution, the major product is the product formed through homo-



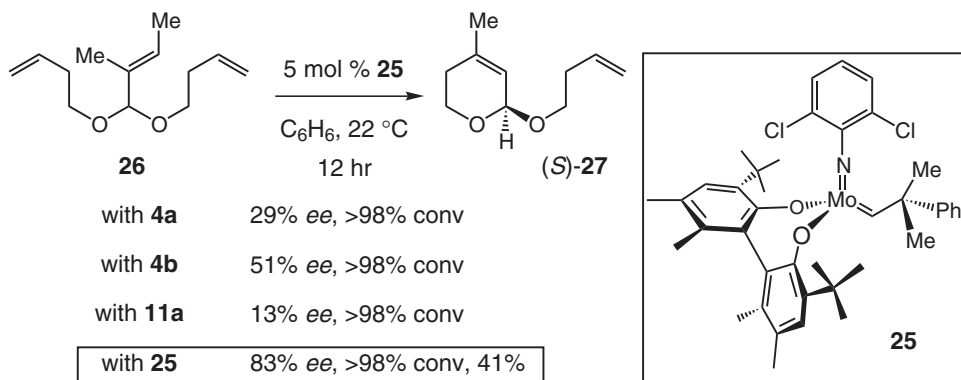
Scheme 2.3-5. Mo-catalyzed desymmetrization of *meso* tetraenes proceeds to afford optically pure heterocycles.

metathesis of the terminal alkenes. The absence of homodimer generation when **11a** is used, particularly when reactions are carried out neat, bears testimony to the high degree of catalyst-substrate specificity in these reactions.

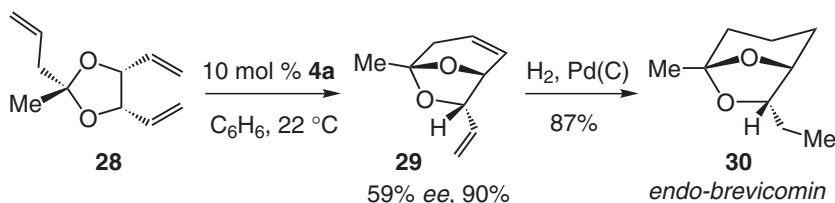
The catalytic desymmetrization shown in Scheme 2.3-5 involves a *meso*-tetraene substrate: optically pure unsaturated siloxane **23** is obtained in $>99\%$ *ee* and 76% yield [16]. The unreacted siloxy ether moiety is removed to deliver optically pure **24**. Mo alkylidenes derived from both enantiotopic terminal alkenes in **22** are likely formed. Since metal-alkylidene formation is reversible, the major product arises from the rapid RCM of the “matched” segment of the tetraene. If any of the “mismatched” RCM takes place, a subsequent and more facile matched RCM leads to the formation of the *meso*-bicycled product. Such a byproduct is absent from the unpurified mixture containing **23**, indicating the exceptionally high degree of stereodifferentiation induced by the chiral catalyst. As before, **4a** is not effective in promoting ARCM of **22**.

Incorporation of electron-withdrawing groups within either the imido or diolate segments of Mo complexes can result in higher levels of catalytic activity, since the Lewis acidity of the transition metal center is enhanced. As the representative examples in Scheme 2.3-6 outline, such structural modifications can have a profound effect on the levels of enantioselectivity as well. In the desymmetrization of acetal **26**, dichlorophenylimido complex **25** provides substantially higher asymmetric induction than biphen- or binol-based catalysts that carry 2,6-dialkylphenylimido moieties (e.g., **4a**). Acetals of the type represented by **27** in Scheme 2.3-7 retain their stereochemical integrity through various routine laboratory operations (such as silica gel chromatography) and can be readily functionalized to deliver a range of chiral non-racemic functionalized heterocycles [16].

The emerging Mo-catalyzed ARCM technology summarized above has been utilized in a brief and enantioselective total synthesis of *endo*-brevicomine (**30**). The key step, as illustrated in Scheme 2.3-7, is the desymmetrization of achiral triene **28** [17].



Scheme 2.3-6. Chiral complex **25**, bearing a 2,6-dichloro imido ligand is the catalyst of choice for asymmetric synthesis of acetals.

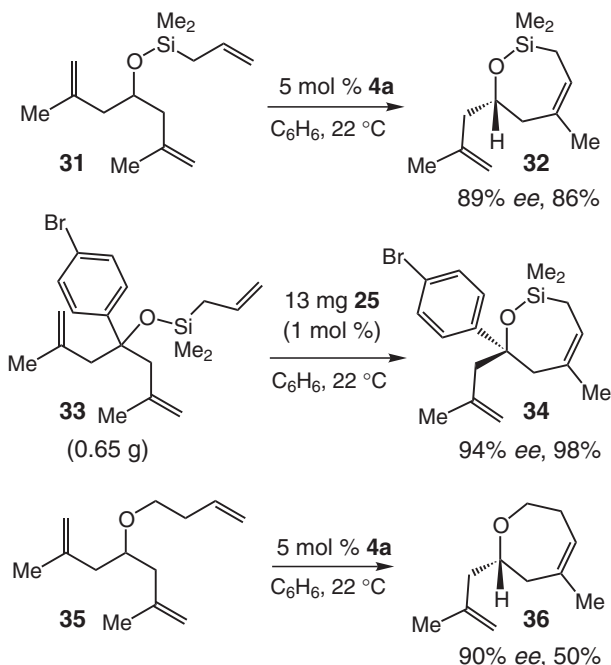


Scheme 2.3-7. Application of Mo-catalyzed ARCM to the synthesis of brevicomin.

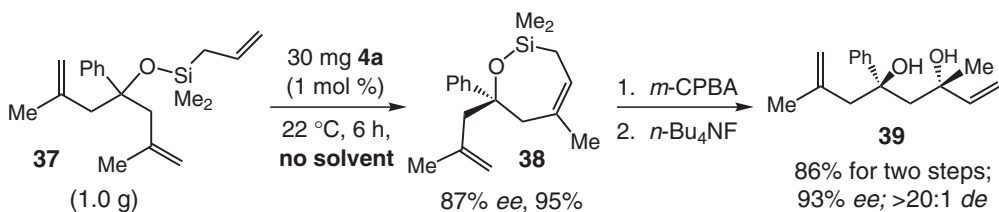
Mo-catalyzed ARCM may be used in the enantioselective synthesis of medium-ring carbo- and heterocycles [18]. As shown in Scheme 2.3-8, medium-ring tertiary siloxanes (e.g., **34**), prepared with high levels of enantioselectivity. These processes can be effected efficiently in preparative scale and at low catalyst loading (e.g., **33** → **34**); such attributes render this catalytic enantioselective method attractive from a practical point of view. It should be noted that in this set of reactions, both **4a** and the dichloroimido complex **25** provide high enantioselectivity. However, the more active **25** is preferable when lower catalyst loadings are required.

The representative transformation in Scheme 2.3-9 illustrates that the optically enriched siloxanes obtained by Mo-catalyzed ARCM can be further functionalized to afford tertiary alcohols (e.g., **39**) with excellent enantio- and diastereomeric purity. It should be noted that conversion of **37** to **38** in Scheme 2.3-9 is carried out without solvent, at 1 mol% catalyst loading and on one gram scale (only 30 mg of catalyst **4a** needed) [18].

More recent studies indicate that ARCM can be used to synthesize small- and medium-ring, N-containing unsaturated heterocycles in high yield and enantioselectivity through catalytic kinetic resolution and asymmetric synthesis [19]. Levels of optical purity can vary depending on the nature of the arylamine (compare **44** with **46** in Scheme 2.3-10). As the synthesis of **48** indicates (cf. Scheme 2.3-10), the



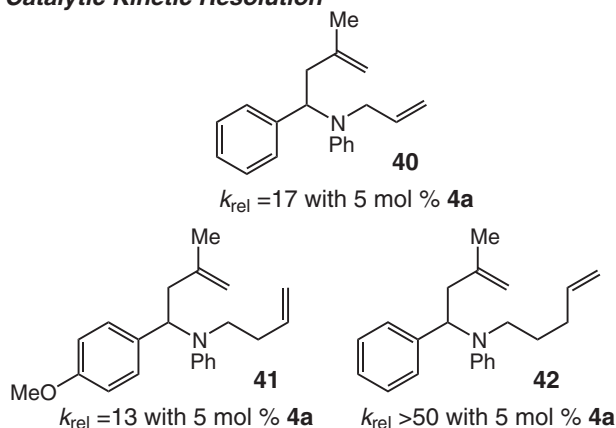
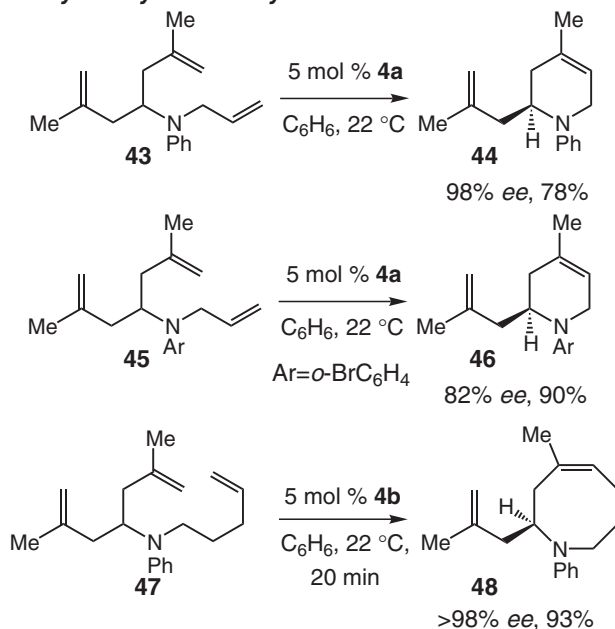
Scheme 2.3-8. Mo-catalyzed tandem ARCM can be used to synthesize seven-membered carbo- and heterocyclic structures efficiently and in optically enriched form.



Scheme 2.3-9. Mo-catalyzed tandem ARCM can be used to synthesize synthetically versatile intermediates such as 1,3-tertiary diols in high enantio- and diastereopurity.

facility and selectivity with which medium-ring unsaturated amines are obtained by the Mo-catalyzed protocol are particularly noteworthy.

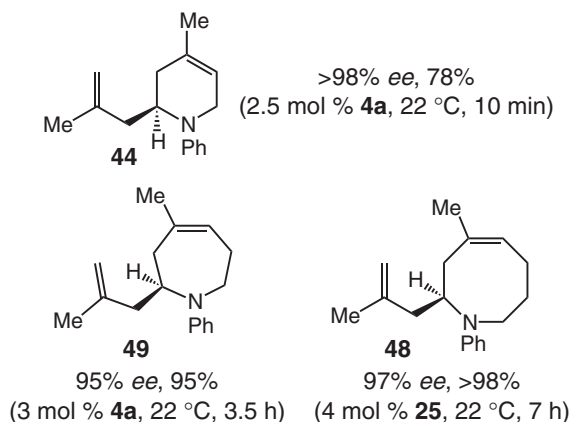
Unlike reactions of carbocyclic and oxygen-containing heterocycles, catalytic enantioselective synthesis of 8-membered ring amines not only proceeds efficiently and with excellent enantioselectivity but also can be carried out in the absence of solvent. Representative data regarding catalytic enantioselective synthesis of various N-containing heterocycles is depicted in Scheme 2.3-11. This remarkably efficient and enantioselective method, which does not require the use of solvent, again highlights the ability of asymmetric metathesis to deliver synthetically versatile materials that are otherwise difficult to prepare.

Catalytic Kinetic Resolution**Catalytic Asymmetric Synthesis****Scheme 2.3-10.** Enantioselective synthesis of amines through Mo-catalyzed ARCM.

2.3.4.5

Catalytic Asymmetric Synthesis Through Tandem Mo-Catalyzed AROM/RCM

The appreciable levels of asymmetric induction observed in the catalytic ARCM reactions discussed above suggest a high degree of enantiodifferentiation in the association of olefinic substrates to chiral Mo complexes. Such stereochemical induction may be exploited in asymmetric ring-opening metathesis (AROM). Cat-



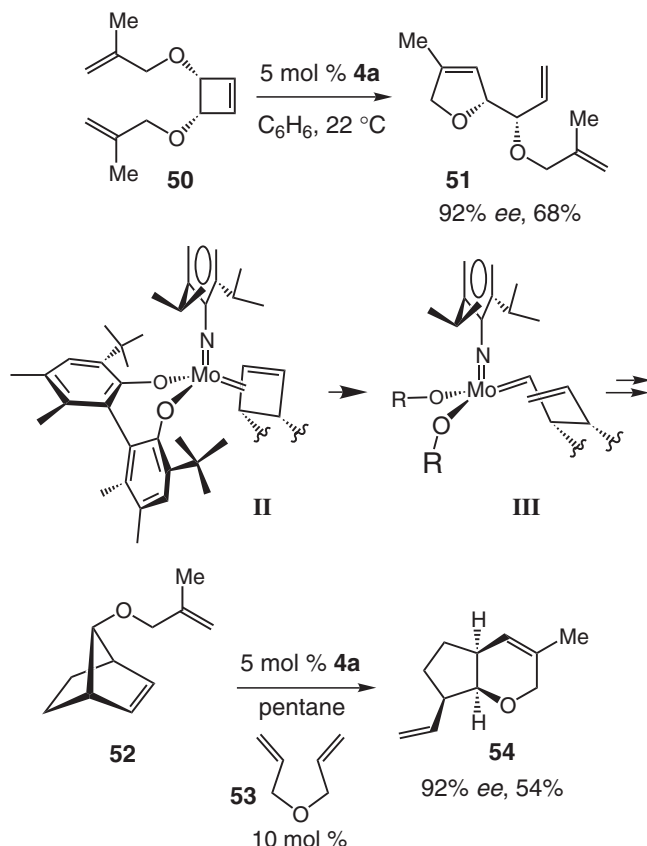
Scheme 2.3-11. Catalytic enantioselective synthesis of amines in the absence of solvent through Mo-catalyzed ARCM.

alytic ROM transformations [20] – although less explored than the related RCM processes – offer unique and powerful methods for the preparation of complex molecules in a single step [2d,g]. The chiral Mo alkylidenes that are products of AROM can be trapped either intramolecularly (RCM) or intermolecularly (cross-metathesis, CM) to afford an assortment of optically enriched compounds.

Transformations shown in Schemes 2.3-12 through 2.3-14 constitute the first examples of catalytic AROM reactions reported. *meso*-Triene **50** is converted to chiral heterocyclic triene **51** in 92% *ee* and 68% yield with 5 mol% **4a** (Scheme 2.3-12) [21]. Presumably, stereoselective approach of the more reactive cyclobutenyl alkene in the manner shown in Scheme 2.3-12 (II) leads to the enantioselective formation of Mo alkylidene **III**, which in turn reacts with an adjacent terminal olefin to deliver **51**. Another example in Scheme 2.3-12 involves the net rearrangement of *meso*-bicycle **52** to bicyclic structure **54** in 92% *ee* and 54% yield. The reaction is promoted by 5 mol% **4a** and requires the presence of diallyl ether **53** [22]. Mechanistic studies suggest that initial reaction of **53** with **4a** leads to the formation of the substantially more reactive chiral Mo=CH₂ complex (vs. neophylidene **4a**), which can react with the sterically hindered norbornyl alkene to initiate the catalytic cycle.

In contrast to **52** (Scheme 2.3-12), diastereomer **55** (Scheme 2.3-13), because of its more exposed and highly reactive strained olefin, undergoes rapid polymerization in the presence of **4a**. The achiral Ru complex **56** [23], however, can be used under an atmosphere of ethylene to effect a tandem ROM/CM to generate **57**. The resulting triene can be subsequently induced to undergo Mo-catalyzed ARCM (5 mol% **4a**) to afford optically pure **58**, the AROM/RCM product that would be directly obtained from **55**.

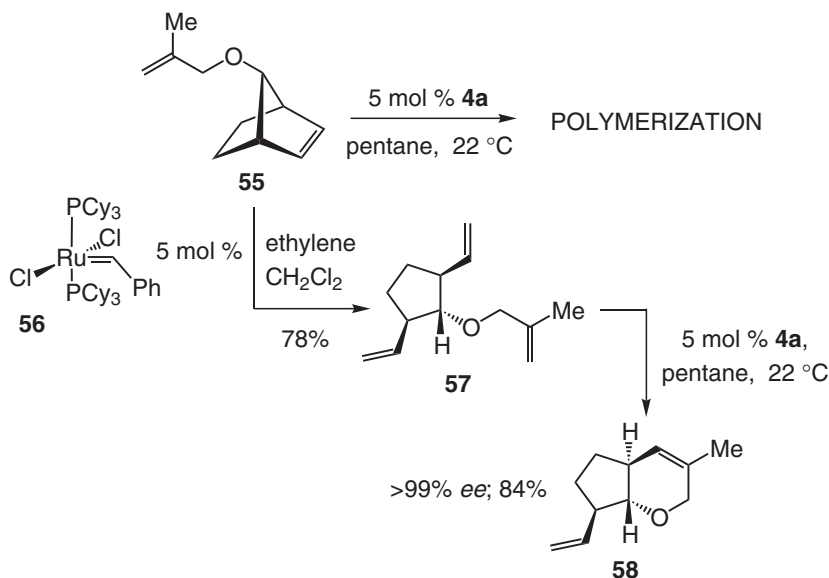
The Mo-catalyzed transformations shown in Scheme 2.3-14 can also be viewed as AROM/RCM processes [24]. However, it is possible that the initial reaction occurs at the terminal olefin, followed by an ARCM involving the cyclic alkene. Regardless of the attendant mechanistic possibilities, the enantioselective re-



Scheme 2.3-12. Mo-catalyzed tandem AROM/RCM allows access to complex heterocyclic structures efficiently and in optically enriched form.

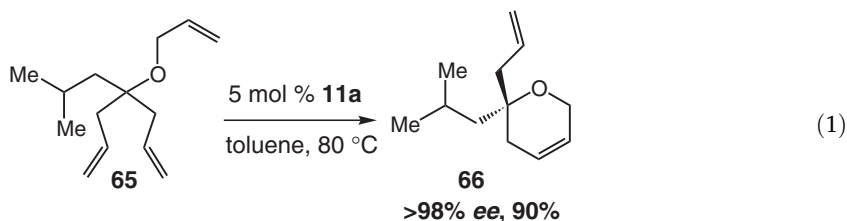
arrangements shown in Scheme 2.3-14, catalyzed by binaphtholate-based catalyst **11a**, deliver unsaturated pyrans bearing a tertiary ether site with excellent efficiency and enantioselectivity. It should be noted that this class of heterocycles would not be readily accessible by an enantioselective synthesis of the precursor diene, followed by RCM promoted by an achiral catalyst. The requisite optically enriched pure tertiary ether or alcohol cannot be easily accessed. It also merits mention that in this class of asymmetric reactions, biphenolate-based complexes provide significantly lower levels of asymmetric induction (e.g., **4a** affords **60** in 15% *ee*). The enantioselective synthesis of the pyran portion of the anti-HIV agent tipranavir (Scheme 2.3-14) serves to demonstrate the significant potential of the method in asymmetric synthesis of biomedically important agents.

The non-racemic pyrans shown in Scheme 2.3-14 can also be accessed by Mo-catalyzed ARCM of the corresponding trienes. The example shown in Eq. (1) is illustrative. Elevated temperatures are required for high levels of enantioselectivity;

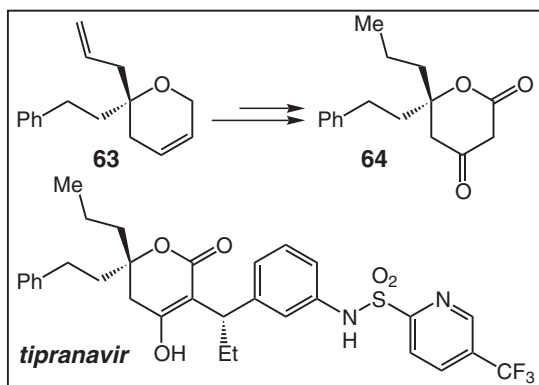
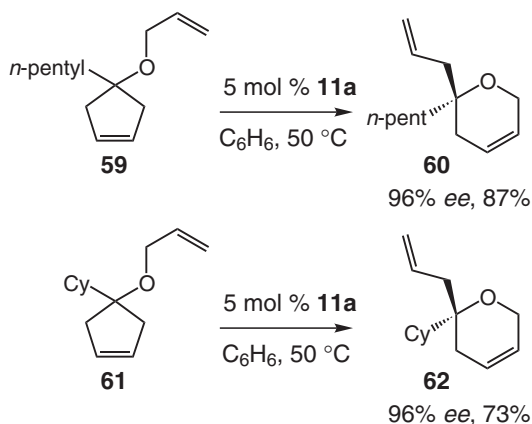


Scheme 2.3-13. Ru complex **56** (ROM) is used in conjunction with chiral catalyst **4a** (ARCM) to obtain **58** in the optically pure form.

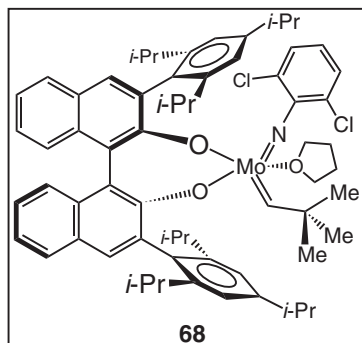
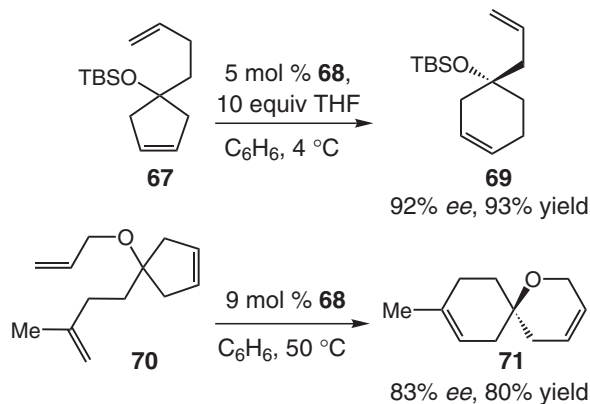
under conditions shown in Scheme 2.3-14, trienes such as **65** afford the desired pyrans in significantly lower *ee* (e.g., **66** is obtained in 30% *ee* at 50 °C). Detailed mechanistic studies need to be carried out before the origin of such variations in selectivity is understood.



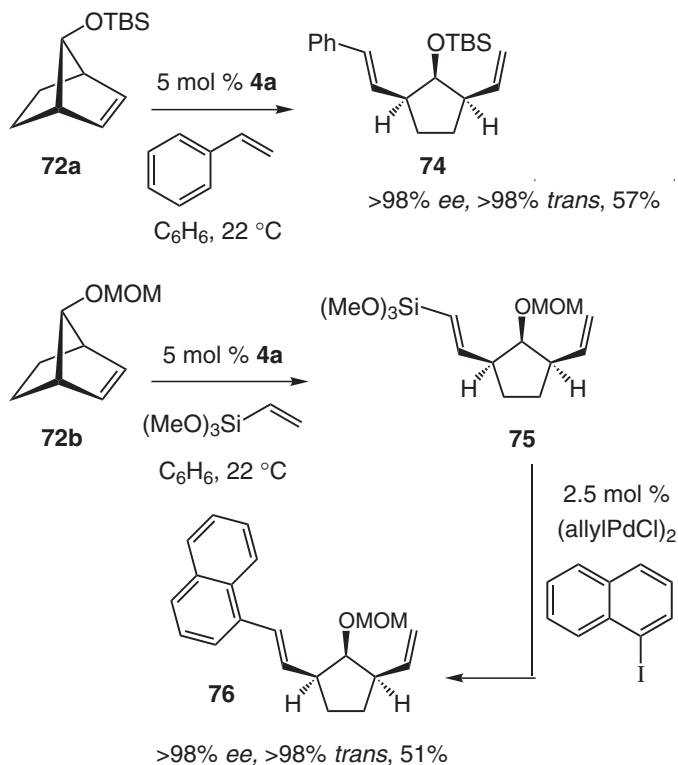
A process related to those shown in Scheme 2.3-14 involves the asymmetric Mo-catalyzed conversion of tertiary carbocyclic cyclopentenyl ethers to the corresponding cyclohexenyl ethers with enantioselectivity (e.g., **67** → **69**, Scheme 2.3-15) [25]. A remarkable and unusual attribute of this class of transformations is that significantly higher levels of enantioselectivity are observed when 10 substrate equivalents of THF are used as an additive. As an example, **69** (Scheme 2.3-15) is formed in only 58% *ee* in the absence of THF (<5% conversion is observed when THF is used as solvent). As also shown in Scheme 2.3-15 (**70** → **71**), enantioenriched spirocycles may be accessed easily by a similar approach; in this case, no additive effect is observed.



Scheme 2.3-14. Mo-catalyzed enantioselective rearrangement of *meso*-cyclopentenes to chiral unsaturated pyrans.



Scheme 2.3-15. Enantioselective synthesis of carbocyclic tertiary ethers and spirocycles through Mo-catalyzed asymmetric olefin metathesis.



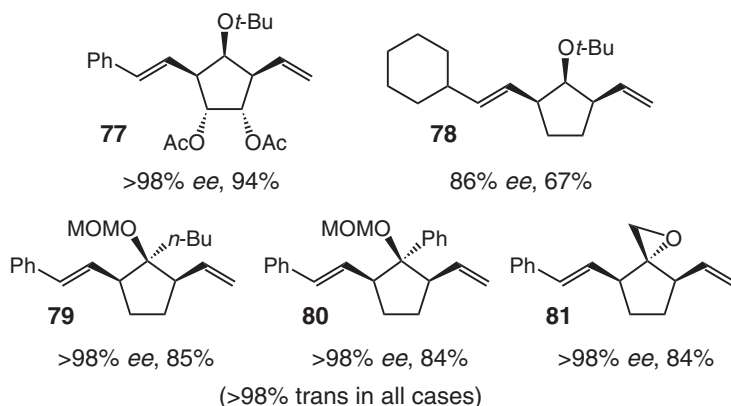
Scheme 2.3-16. Mo-catalyzed tandem AROM/CM proceeds with high enantioselectivity and olefin stereocontrol.

2.3.4.6

Catalytic Asymmetric Synthesis Through Tandem Mo-Catalyzed AROM/CM

The chiral Mo-alkylidene complex derived from AROM of a cyclic olefin also may participate in an intermolecular cross-metathesis reaction. As depicted in Scheme 2.3-16, treatment of *meso*-72a with a solution of 5 mol% **4a** and 2 equivalents of styrene leads to the formation of optically pure **74** in 57% isolated yield and $>98\%$ *trans* olefin selectivity [26]. The Mo-catalyzed AROM/CM reaction can be carried out in the presence of vinylsiloxanes: the derived optically pure **74** (Scheme 2.3-16) can subsequently be subjected to Pd-catalyzed cross-coupling reactions, allowing access to a range of optically pure cyclopentanes.

The Mo-catalyzed AROM/CM can be performed on functionalized norbornyl substrates (e.g., **77** and **78**, Scheme 2.3-17) and those that bear tertiary ether sites (e.g., **79–81**, Scheme 2.3-17). Initial studies indicate that the relative orientation of the heteroatom substituent versus the reacting olefin can have a significant influence on reaction efficiency. Nevertheless, the products shown in Scheme 2.3-16 represent versatile synthetic intermediates accessed in the optically pure form by Mo-catalyzed AROM/CM.



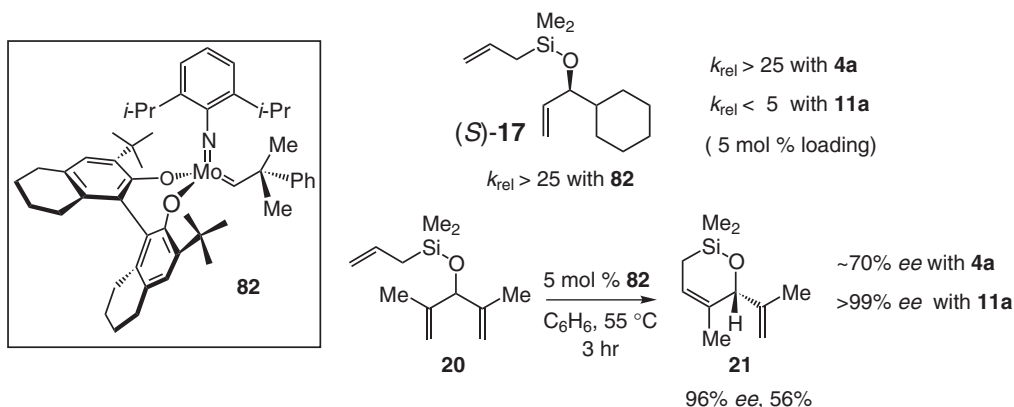
Scheme 2.3-17. Mo-catalyzed tandem AROM/CM delivers highly functionalized cyclopentanes in optically pure form.

2.3.4.7

Towards User-Friendly and Practical Chiral Mo-Based Catalysts for Olefin Metathesis

Although the main focus of our programs has been on issues of reactivity and enantioselectivity, we have recently begun to address the important issue of practicality in Mo-catalyzed asymmetric metathesis. Two key advances have been reported in this connection: (1) the availability of chiral Mo catalysts that can be prepared *in situ* from commercially available compounds, and (2) the synthesis of a recyclable polymer-supported chiral Mo catalyst. These advances are summarized below.

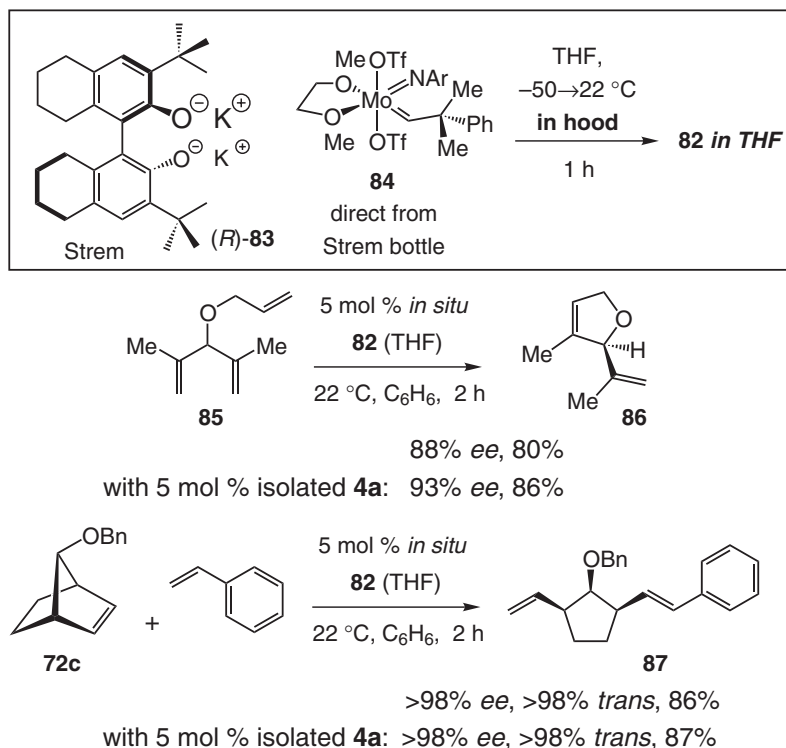
Up to this point, there have been two general classes of chiral Mo catalysts discussed: biphenolate-based complexes such as **4** and binaphtholate systems represented by **11** (Scheme 2.3-2). From a practical point of view, binaphthol-based systems have a significant advantage, as the synthesis of the optically pure diolate begins from the inexpensive and commercially available (*R*)- or (*S*)-binaphthol. Access to the optically pure biphenol ligand in **4** and its derivatives requires resolution of the racemic material by fractional crystallization of the derived phosphorus(V) mentholates [2]. Accordingly, we prepared chiral Mo complex **82** [27], bearing a “biphenol-type” ligand, but synthesized from the readily available optically pure binaphthol. Complex **82** shares structural features with both the biphen- (**4**) and binol-based (**11**) systems and represents an intriguing possibility regarding the range of starting materials for which it may be a suitable catalyst. Two examples are depicted in Scheme 2.3-18. Catalyst **82** delivers compounds of high optical purity where either biphen- or binol-based complexes are ineffective. It is not in all instances that **82** operates as well as **4a** and **11a**. As an example, in the presence of 5 mol% **82**, triene **18** (Scheme 2.3-4) is converted to furan **19** in 77% ee and 73% yield (vs. 99% ee and 93% yield with **4a**). It should be noted that catalyst **71** serves as an additional example, where modification of the chiral alkoxide ligand can lead to substantial variation in selectivity.



Scheme 2.3-18. Chiral complex **82** represents a hybrid between biphen- and binol-based catalysts and provides a unique selectivity profile that is often not seen with the latter two classes individually.

That catalyst **82** is more easily prepared than **4** is not its only advantage. As illustrated in Scheme 2.3-19, a solution of **82**, obtained by reaction of the commercially available reagents bis(potassium salt) **83** and Mo triflate **84** (both commercially available from Strem), can be used directly to promote enantioselective metathesis. Similar levels of reactivity and selectivity are obtained with both *in situ* **82** and isolated and purified **4a** or **82** (cf. Scheme 2.3-18). Moreover, asymmetric olefin metatheses proceed with equal efficiency and selectivity with the same stock solutions of (*R*)-**83** and **84** after 2 weeks. The use of a glove box, Schlenk equipment, or vacuum lines is not necessary (even with the 2-week-old solutions). The *in situ* catalyst preparation procedure can be readily applied to other chiral Mo complexes as well [25].

We have synthesized and studied the activity of **89**, the first supported chiral catalyst for olefin metathesis (Scheme 2.3-20) [28]. Catalyst **89** efficiently promotes a range of ARCM and AROM processes; a representative example is shown in Scheme 2.3-20. Rates of reaction are lower than those observed with the corresponding monomeric complex **4a**, but similar levels of enantioselectivity are observed. Although **89** must be kept under dry and oxygen-free conditions, it can be recycled. Catalyst activity, however, is diminished by the third cycle. As the data and the figure in Scheme 2.3-20 show, the product solution obtained by filtration contains significantly lower levels of metal impurity than detected with the monomeric catalysts, where >90% of the Mo used is found in the unpurified product (by ICP-MS analysis). The supported chiral Mo catalyst is, as should perhaps be expected, less active than the parent system (**4a**). The lower levels of activity exhibited by **89** are perhaps due to inefficient diffusion of substrate molecules into the polymer. The supported catalyst is expected to be less susceptible to bimo-



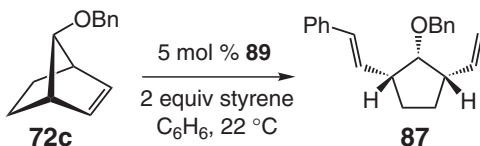
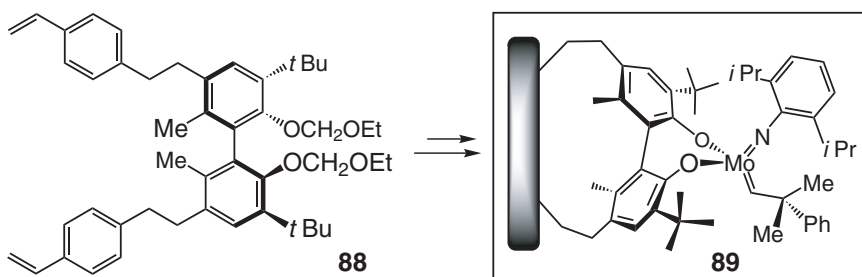
Scheme 2.3-19. *In situ* preparation and utility of chiral metathesis catalyst **82**.

lecular decomposition of highly reactive methylidene intermediates [29]. Synthesis of more rigid polymer supports or those that represent lower Mo loading should minimize bimolecular decomposition and lead to a more robust class of catalysts.

2.3.5

Chiral Ru-Based Olefin Metathesis Catalysts

Grubbs and coworkers have reported a new class of Ru catalysts (**90**, Eq. (2)) [30] that bear a chiral monodentate N-heterocyclic carbene ligand [31]. The reactions illustrated in Eq. 2 include the highest *ee* reported in the study (13–90% *ee*). Asymmetric induction is dependent on the degree of olefin substitution (cf. Schemes 2.3-4 and 2.3-19 for comparison with the Mo-catalyzed reactions of the same substrates). As is the case with nearly all catalytic enantioselective reactions [4], the identity of the optimal catalyst depends on the substrate. Therefore, a number of chiral Ru catalysts were prepared and screened before **90** was identified as the most suitable. In addition, reactions were shown to be more selective in the presence of NaI.

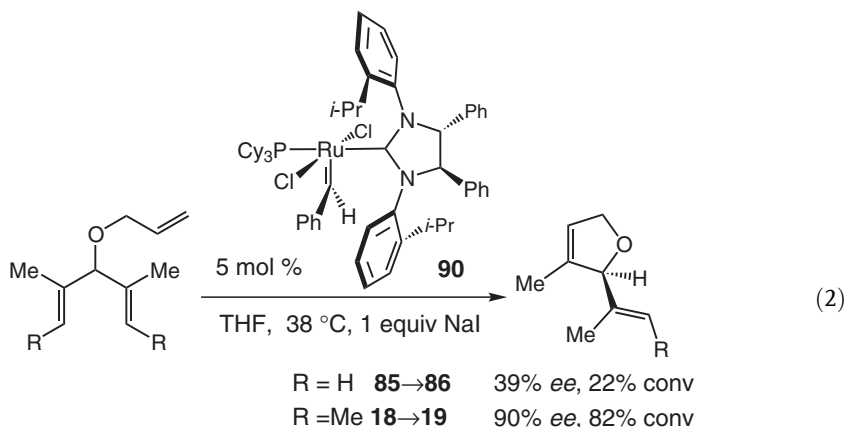


Cycle 1: >98% conv, 30 min; 97% *ee*
product contains 3% of total Mo initially used

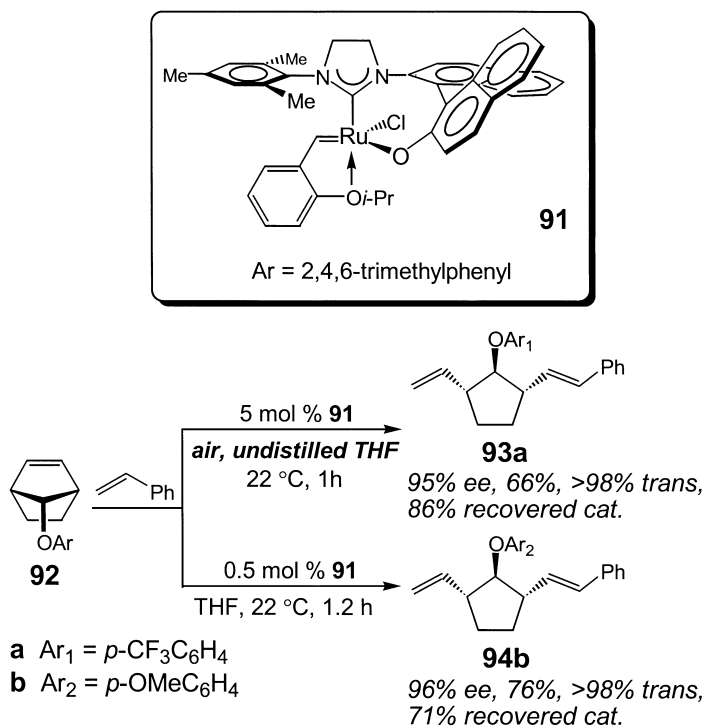
Cycle 2: 98% conv, 30 min; 98% *ee*
product contains 10% of total Mo initially used

Cycle 3: 55% conv, 16 h; 89% *ee*
product contains 16% of total Mo initially used

Scheme 2.3-20. The first recyclable and supported chiral catalyst for olefin metathesis, **89** delivers reaction products that contain significantly less metal impurity. The two dram vials show unpurified **87** from a reaction catalyzed by **4a** (left) and **89** (right).



Most recently, we have reported the synthesis and structure of a new chiral bidentate imidazolium ligand and a derived chiral Ru-based carbene **91** (Scheme 2.3-21) [32]. Chiral Ru complex **91** is stereogenic at the metal center and can be



Scheme 2.3-21. Air stable chiral Ru-based catalyst for olefin metathesis can be used for highly effective and selective AROM/CM reactions.

prepared in >98% diastereoselectivity and purified by silica gel chromatography with undistilled solvents. This air-stable styrene-ether Ru complex, which is based on related achiral complexes developed earlier in our laboratories [33], efficiently catalyzes ring-closing and ring-opening metathesis and is recyclable. As the representative cases in Scheme 2.3-21 illustrate, the chiral complex is highly effective (0.5–10 mol% loading) in promoting enantioselective ring-opening/cross-metathesis reactions (up to >98% ee). These enantioselective transformations can be effected in air (cf. Scheme 2.3-21), with unpurified solvent, and with substrates that would only polymerize with chiral Mo-based catalysts.

2.3.6

Conclusions and Outlook

The exciting results of the above investigations clearly indicate that the modular Mo-based construct initially reported for catalyst **1** can be exploited to generate a range of highly efficient and selective chiral catalysts for olefin metathesis. Both

ARCM and AROM reactions can be promoted by these chiral catalysts to obtain optically enriched or pure products that are typically unavailable by other methods or that can be accessed only by significantly longer routes. Substantial variations in reactivity and selectivity arising from subtle changes in catalyst structures support the notion that synthetic generality is more likely if a range of chiral complexes is available [4].

The chiral Mo-based catalysts discussed herein are more sensitive to moisture and air than the related Ru-based catalysts [1]. However, these complexes remain the most effective general asymmetric metathesis catalysts and are significantly more robust than the original hexafluoro-Mo complex **1**. It should be noted that chiral Mo-based catalysts **4**, **11**, **25**, **68**, and **82** can be easily handled on a large scale. In the majority of cases, reactions proceed readily to completion in the presence of only 1 mol% catalyst, and, in certain cases, optically pure materials can be accessed within minutes or hours in the absence of solvents. Little or no solvent waste products need to be dealt with upon obtaining optically pure materials. Complex **4a** is commercially available from Strem, Inc. (both antipodes and racemic). The advent of the protocols for *in situ* preparation of chiral Mo catalyst **82**, the supported and recyclable complex **89**, and the emergence of chiral Ru-based catalysts **90** and **91** bode well for future development of practical chiral metathesis catalysis. The above attributes collectively render these new classes of chiral catalysts extremely attractive for future applications in efficient, catalytic, enantioselective, and environmentally conscious protocols in organic synthesis.

Acknowledgments

I am grateful to my collaborator, Professor Richard R. Schrock, and all the co-workers whose names appear in the references for invaluable intellectual and experimental contributions. Financial support was provided by the National Institutes of Health (GM-59426) and the National Science Foundation (CHE-9905806 and CHE-0213009 to A. H. H.).

References

- 1 For select reviews on catalytic olefin metathesis, see: a) R. H. GRUBBS, S. CHANG, *Tetrahedron* **1998**, *54*, 4413–4450; b) A. FÜRSTNER, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043.
- 2 For example, see: a) A. F. HOURI, Z. XU, D. A. COGAN, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1995**, *117*, 2943–2944; b) Z. XU, C. W. JOHANNES, A. F. HOURI, D. S. LA, D. A. COGAN, G. E. HOFILENA, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316; c) D. MENG, D.-S. SU, A. BALOG, P. BERTINATO, E. J. SORENSEN, S. J. DANISHEFSKY, Y.-H. ZHENG, T.-C. CHOU, L. HE, S. B. HORWITZ, *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734; d) K. C. NICOLAOU, N. WINSSINGER, J. PASTOR, S. NINKOVIC, F. SARABIA, Y. HE, D. VOURLOUMIS, Z. YANG, T. LI, P. GIANNAKAKOU, E. HAMEL, *Nature* **1997**, *387*, 268–272; e) C. W. JOHANNES, M. S. VISSER, G. S. WEATHERHEAD, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1998**, *120*, 8340–8347; f) M. DELGADO, J. D. MARTIN, *J. Org. Chem.* **1999**, *64*, 4798–4816; g) A. FÜRSTNER, O. R. THIEL, *J. Org. Chem.*

- 2000, 65, 1738–1742; h) J. LIMANTO, M. L. SNAPPER, *J. Am. Chem. Soc.* **2000**, 122, 8071–8072; i) A. B. SMITH, S. A. KOZMIN, C. M. ADAMS, D. V. PAONE, *J. Am. Chem. Soc.* **2000**, 122, 4984–4985.
- 3 a) R. R. SCHROCK, J. S. MURDZEK, G. C. BAZAN, J. ROBBINS, M. DiMARE, M. O'REGAN, *J. Am. Chem. Soc.* **1990**, 112, 3875–3886; b) G. C. BAZAN, J. H. OSKAM, H.-N. CHO, L. Y. PARK, R. R. SCHROCK, *J. Am. Chem. Soc.* **1991**, 113, 6899–6907.
 - 4 a) K. W. KUNTZ, M. L. SNAPPER, A. H. HOVEYDA, *Curr. Opin. Chem. Biol.* **1999**, 3, 313–319; b) K. D. SHIMIZU, M. L. SNAPPER, A. H. HOVEYDA, In *Comprehensive Asymmetric Catalysis I–III*; E. N. JACOBSEN, A. PFALTZ, H. YAMAMOTO, Eds.; Springer: Berlin, 1999; Vol. 3, 1389–1399; For a areport regarding synthesis of various Mo complexes, see: c) J. H. OSKAM, H. H. FOX, K. B. YAP, D. H. MCCONVILLE, R. O'DELL, B. J. LICHTENSTEIN, R. R. SCHROCK, *J. Organomet. Chem.* **1993**, 459, 185–198.
 - 5 For a brief overview of this Mo-catalyzed asymmetric olefin metathesis, see: A. H. HOVEYDA, R. R. SCHROCK, *Chem. Eur. J.* **2001**, 7, 945–950.
 - 6 For early reports regarding the preparation of chiral Mo-based catalysts used for ROMP, see: a) D. H. MCCONVILLE, J. R. WOLF, R. R. SCHROCK, *J. Am. Chem. Soc.* **1993**, 115, 4413–4414; b) K. M. TOTLAND, T. J. BOYD, G. G. LAVOIE, W. M. DAVIS, R. R. SCHROCK, *Macromolecules* **1996**, 29, 6114–6125.
 - 7 Throughout this article, the identity of the recovered enantiomer shown is that which is obtained by the catalyst antipode illustrated. Moreover, transformations with binol-based complexes (e.g., 11) were carried out with the opposite antipode of the catalyst versus that illustrated. Because (*S*)-biphen and (*R*)-binol complexes were employed in our studies, this adjustment has been made to facilitate comparison between biphen- and binol-based catalysts.
 - 8 a) O. FUJIMURA, R. H. GRUBBS, *J. Am. Chem. Soc.* **1996**, 118, 2499–2500; b) O. FUJIMURA, R. H. GRUBBS, *J. Org. Chem.* **1998**, 63, 824–832.
 - 9 For a review on metal-catalyzed kinetic resolution, see: A. H. HOVEYDA, M. T. DIDIUK, *Curr. Org. Chem.* **1998**, 2, 537–574.
 - 10 J. B. ALEXANDER, D. S. LA, D. R. CEFALO, A. H. HOVEYDA, R. R. SCHROCK, *J. Am. Chem. Soc.* **1998**, 120, 4041–4042.
 - 11 The value for k_{rel} is calculated by the equation reported by Kagan: H. B. KAGAN, J. C. FIAUD, *Top. Stereochem.* **1988**, 53, 708–710.
 - 12 D. S. LA, J. B. ALEXANDER, D. R. CEFALO, D. D. GRAF, A. H. HOVEYDA, R. R. SCHROCK, *J. Am. Chem. Soc.* **1998**, 120, 9720–9721.
 - 13 a) J. H. OSKAM, R. R. SCHROCK, *J. Am. Chem. Soc.* **1993**, 115, 11831–11845; b) H. H. FOX, M. H. SCHOFIELD, R. R. SCHROCK, *Organometallics* **1994**, 13, 2804–2816.
 - 14 SCHROCK, R. R. *Polyhedron* **1995**, 14, 3177–3195; b) WU, Y.-D., PENG, Z.-H. *J. Am. Chem. Soc.* **1997**, 119, 8043–8049.
 - 15 S. S. ZHU, D. R. CEFALO, D. S. LA, J. Y. JAMIESON, W. M. DAVIS, A. H. HOVEYDA, R. R. SCHROCK, *J. Am. Chem. Soc.* **1999**, 121, 8251–8259.
 - 16 G. S. WEATHERHEAD, J. H. HOUSER, G. J. FORD, J. Y. JAMIESON, R. R. SCHROCK, A. H. HOVEYDA, *Tetrahedron Lett.* **2000**, 41, 9553–9559.
 - 17 S. D. BURKE, N. MULLER, C. M. BEUDRY, *Org. Lett.* **1999**, 1, 1827–1829.
 - 18 a) A. F. KIELY, J. A. JERNELIUS, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2002**, 124, 2868–2869.
 - 19 S. J. DOLMAN, E. S. SATTELY, A. H. HOVEYDA, R. R. SCHROCK, *J. Am. Chem. Soc.* **2002**, 124, 6991–6997.
 - 20 For representative studies regarding non-asymmetric ROM reactions, see: a) M. L. RANDALL, J. A. TALLARICO, M. L. SNAPPER, *J. Am. Chem. Soc.* **1995**, 117, 9610–9611; b) W. J. ZUERCHER, M. HASHIMOTO, R. H. GRUBBS, *J. Am. Chem. Soc.* **1996**, 118, 6634–6640; c) J. P. A. HARRITY, M. S. VISSER, J. D. GLEASON, A. H.

- HOVEYDA, J. *Am. Chem. Soc.* **1997**, *119*, 1488–1489; d) M. F. SCHNEIDER, N. LUCAS, J. VELDER, S. BLECHERT, *Angew. Chem. Int. Ed.* **1997**, *36*, 257–259; e) F. D. CUNY, J. CAO, J. R. HAUSKE, *Tetrahedron Lett.* **1997**, *38*, 5237–5240.
- 21 G. S. WEATHERHEAD, J. G. FORD, E. J. ALEXANIAN, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2000**, *122*, 8071–8072.
- 22 J. P. A. HARRITY, D. S. LA, D. R. CEFALO, M. S. VISSER, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1998**, *120*, 2343–2351.
- 23 P. SCHWAB, M. B. FRANCE, J. W. ZILLER, R. H. GRUBBS, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039–2041.
- 24 D. R. CEFALO, A. F. KIELY, M. WUCHRER, J. Y. JAMIESON, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2001**, *123*, 3139–3140.
- 25 X. TENG, D. CEFALO, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2002**, *124*, 10779–10784.
- 26 D. S. LA, G. J. FORD, E. S. SATTELY, P. J. BONITATEBUS, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1999**, *121*, 11603–11604.
- 27 S. L. AEILTS, D. R. CEFALO, P. J. BONITATEBUS, JR., J. H. HOUSER, A. H. HOVEYDA, R. R. SCHROCK, *Angew. Chem. Int. Ed.* **2001**, *40*, 1452–1456.
- 28 K. C. HULTSZCH, J. A. JERNELIUS, A. H. HOVEYDA, R. R. SCHROCK, *Angew. Chem. Int. Ed.* **2002**, *41*, 589–593.
- 29 J. ROBBINS, G. C. BAZAN, J. S. MURDZEK, M. B. O'REGAN, R. R. SCHROCK, *Organometallics* **1991**, *10*, 2902–2907.
- 30 T. J. SEIDERS, D. W. WARD, R. H. GRUBBS, *Org. Lett.* **2001**, *3*, 3225–3228.
- 31 W. A. HERRMANN, L. J. GOOSSEN, C. KOCHER, G. R. J. ARTUS, *Angew. Chem. Int. Ed.* **1996**, *35*, 2806–2807.
- 32 J. J. VANVELDHUIZEN, S. B. GARBER, J. S. KINGSBURY, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955.
- 33 a) J. P. A. HARRITY, M. S. VISSER, J. D. GLEASON, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1997**, *119*, 1488–1489; b) J. P. A. HARRITY, D. S. LA, D. R. CEFALO, M. S. VISSER, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1998**, *120*, 2343–2351; c) J. S. KINGSBURY, J. P. A. HARRITY, P. J. BONITATEBUS, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1999**, *121*, 791–799; d) S. B. GARBER, J. S. KINGSBURY, B. L. GRAY, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

2.4

Tandem Ring-Closing Metathesis

Stefan Randl and Siegfried Blechert

2.4.1

Introduction

In classical organic synthesis, the individual bonds in the target molecule are usually formed step by step. Starting from relatively simple starting compounds, the structural complexity in the molecule slowly increases in the course of the synthesis. Tandem reactions allow for the rapid construction of complex structures from simple precursors in only one pot. Tandem or domino reactions can be defined as processes that involve at least two transformations in one step, in which the subsequent reaction always occurs at the functionality formed in the previous step. These transformations can be either bond formation or bond cleavage. Apart from the ease of the synthesis, these transformations are also considered favorable from an ecological point of view. The amount of energy and chemical waste can thus be significantly reduced.

Various domino processes are known in nature [1]. These are generally catalyzed by multi-enzymatic systems, which efficiently catalyze each step. Over the last few decades, countless domino reactions have been developed in the laboratory using classical organic reactions [2]. Along with the establishment of olefin metathesis as a standard and versatile reaction in organic synthesis, several tandem reactions involving a metathesis step have been described. Among them, there are sequences that combine a metathesis step with a reaction of a different nature. Combinations with Diels-Alder reactions [3], Pd-catalyzed reactions [4], and sigmatropic rearrangements [5] have been reported, to mention but a few of the various examples.

In this chapter, domino reactions involving metathesis steps only will be discussed, with a particular focus on intramolecular tandem reactions. Oligomerization or polymerization reactions, which can be seen as intermolecular tandem reactions, are dealt with in Chapter IV.

Figure 2.4-1 shows the metathesis catalysts that have been utilized in the reactions described in this chapter. Chiral variants of **Mo** have been employed for desymmetrizing enantioselective domino metathesis reactions of C_5 -symmetrical substrates [6]. These reactions are discussed in Chapter 2.3 (Enantioselective RCM, Hoveyda).

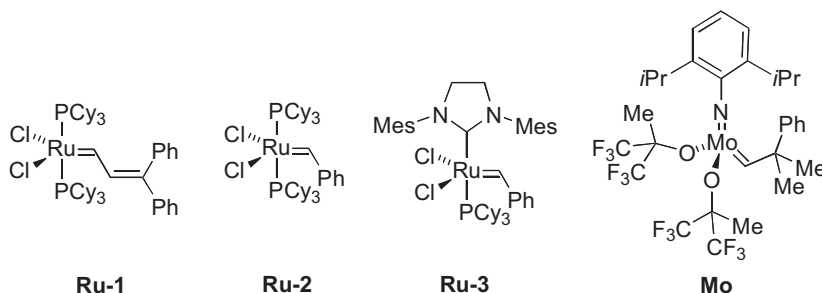
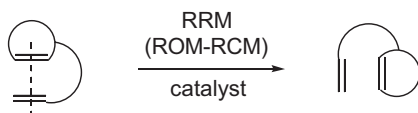


Fig. 2.4-1. Metathesis catalysts (Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl).



Scheme 2.4-1. Ring rearrangement of an alkenyl-substituted cycloolefin.

2.4.2

Tandem Metathesis Involving Double Bonds Only

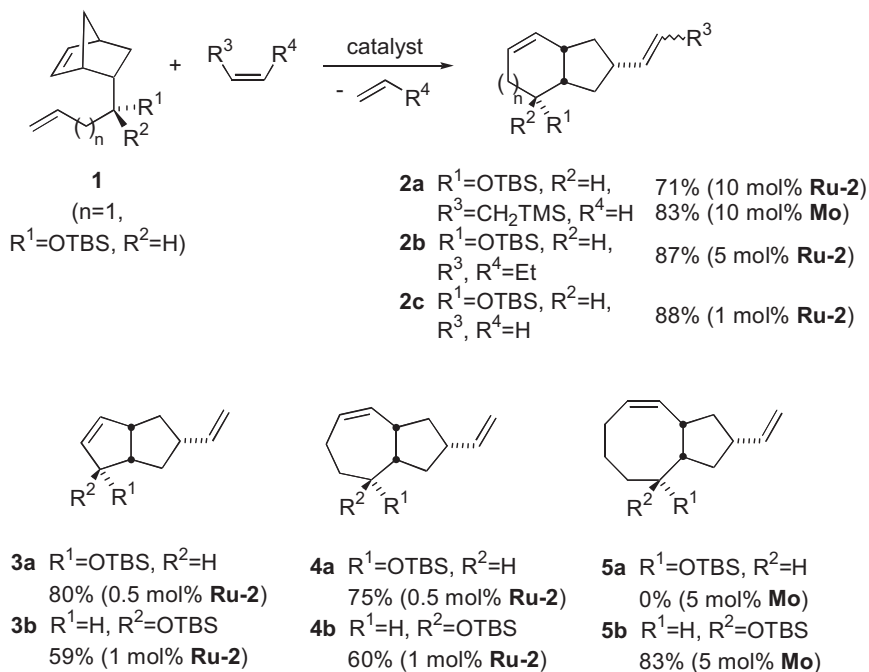
The tandem reactions described in this section involve intramolecular metathesis reactions between an endocyclic olefin and an exocyclic C–C double bond. In such a metathesis step, one ring is opened (ring-opening metathesis [ROM]) and concomitantly a new one is formed (ring-closing metathesis [RCM]). Since the combination of ROM-RCM results in products with a rearranged ring system, these reactions are generally referred to as ring rearrangement metatheses (RRM). The shortest general domino sequence of this type, depicted in Scheme 2.4-1, involves the ring rearrangement of an alkenyl-substituted cycloolefin.

Several examples of double or even triple RCM reactions of tetraenes and hexaenes, respectively, have been described, in which two or more rings were formed in one step from acyclic olefinic precursors [7–9]. These reactions often show remarkable selectivity and have been used in concise syntheses of polycyclic systems. These have often been designated as tandem processes. However, the single RCM steps in these reactions occur independently of one another, and therefore do not comply with the definition of a tandem process as outlined in the introduction and will not be discussed here.

2.4.2.1

RRM of Alkenyl-Substituted Cycloolefins

Norbornenes are known to undergo ring-opening metathesis polymerization (ROMP). In the presence of at least one equivalent of a monosubstituted olefin, ROMP is usually efficiently suppressed and ROM-CM dominates. Alkenyl substituted norbornenes such as **1** are typical examples. In the absence of an added olefin, **1** underwent quantitative ROMP. With an excess of an added acyclic olefin,

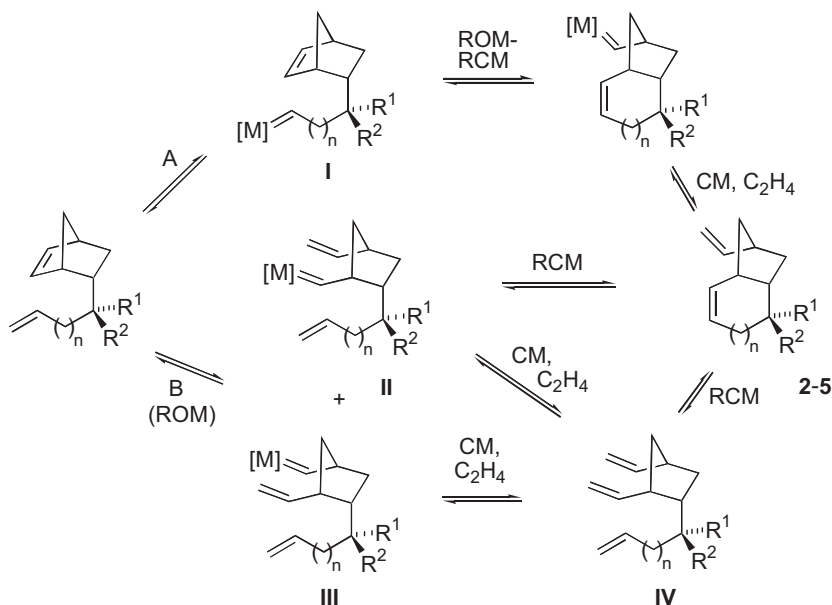


Scheme 2.4-2. ROM-RCM-CM reactions of alkenyl-substituted norbornenes.

ROMP could be efficiently suppressed and hydroindene derivatives **2a–c** were obtained in good yields (Scheme 2.4-2) [10]. These domino metathesis reactions involve ROM of the norbornene, RCM with the terminal double bond, and a CM reaction with the added olefin. As in ROMP or ROM-CM of norbornenes, the release from ring strain of the norbornene is the driving force in these transformations, making them energetically favorable.

Variation of the length of the alkenyl side chain gave rise to bicycles of different ring sizes. Complexes **3–5** are the products of ring rearrangements of the corresponding norbornenes (**1**, $n = 0, 2, 3$) with ethylene. Hydropentalenenes **3** and hydroazulenes **4** were prepared in moderate to good yields. In both cases, a marked influence of the configuration of the stereocenter adjacent to the norbornene on the yield of the rearrangement was observed. The isolation of **5b** proved that even a relatively strained cyclooctene could be formed in this tandem sequence. Whereas the use of **Ru-2** as the catalyst furnished the ring-opened product of general type **IV** (Scheme 2.4-3), only the more reactive **Mo** catalyzed the rearrangement to **5b** efficiently. Also with **Mo**, triene **IV** was shown to be formed first, which was subsequently converted into the ring-rearranged product. Diastereomeric **5a** could not be obtained with either catalyst.

Two principal mechanistic pathways can be taken into account for these domino reactions (Scheme 2.4-3). The first involves initial attack of the metal alkylidene at the exocyclic olefin to afford alkylidene **I**, which then reacts with the endocyclic



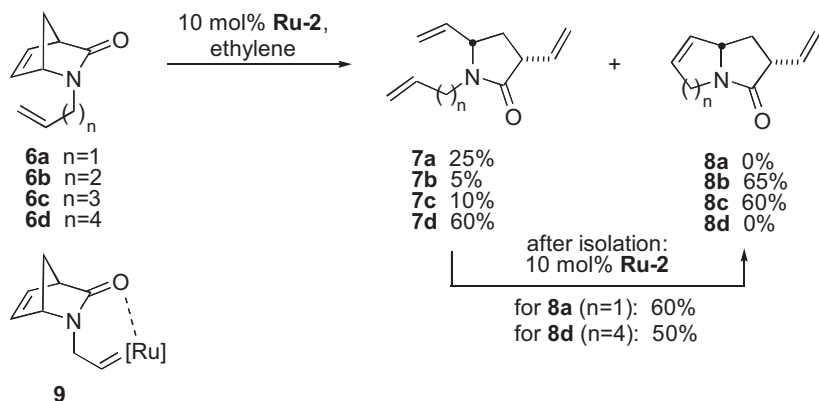
Scheme 2.4-3. Possible mechanistic pathways of RRM of alkenyl-substituted norbornenes with ethylene.

double bond (pathway A). Alternatively, the norbornene may be ring opened first, which would lead to intermediates **II** or **III** (pathway B). In the formation of the [6.3.0] bicyclic **5b**, it looks probable that an initial ROM-CM sequence occurs to afford a triene of type **IV**, which is converted into the product in a subsequent RCM reaction [11, 12].

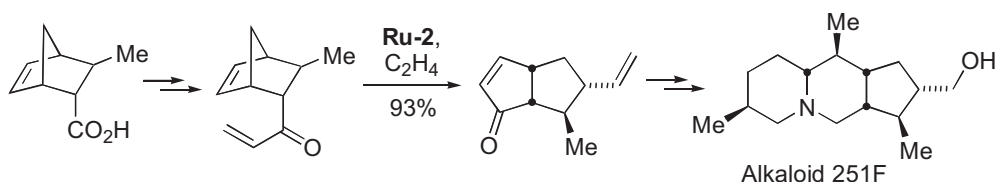
As with all RRM processes, which mechanism is dominant is likely to be dependant on the ring-opening proclivities of the substrate. It would be reasonable to assume that reactions involving more highly strained cycloolefins would proceed *via* pathway B, while less strained substrates would be expected to react initially at the exocyclic alkene.

Plumet *et al.* have used this strategy to prepare azabicyclic γ -lactams starting from (1*S*)-2-azanorborn-5-en-3-ones **6** (Scheme 2.4-4) [13]. Substrates **6b** and **6c** furnished the bicyclic **8b** and **8c** in moderate yields, along with small amounts of products resulting from ROM (**7b,c**). In the case of substrates **6a** and **6d** ($n = 1$ and $n = 4$), no formation of rearranged products was observed and only ring-opened products of type **7** were isolated. Using a variant of **Ru-3** [14] as the catalyst did not provide any rearranged products either. Trienes **7a** and **7d** could be converted into the desired products in a subsequent RCM reaction; however, yields for these two-step procedures were low.

The failure of the ring rearrangement of **6a** may be attributed to a deleterious chelating effect of the carbonyl oxygen, giving rise to alkylidene **9** (see intermediate **I**, Scheme 2.4-3). Its relative stability (and hence metathesis inactivity) could ac-



Scheme 2.4.4. RRM of 2-azanorborn-5-en-3-ones.



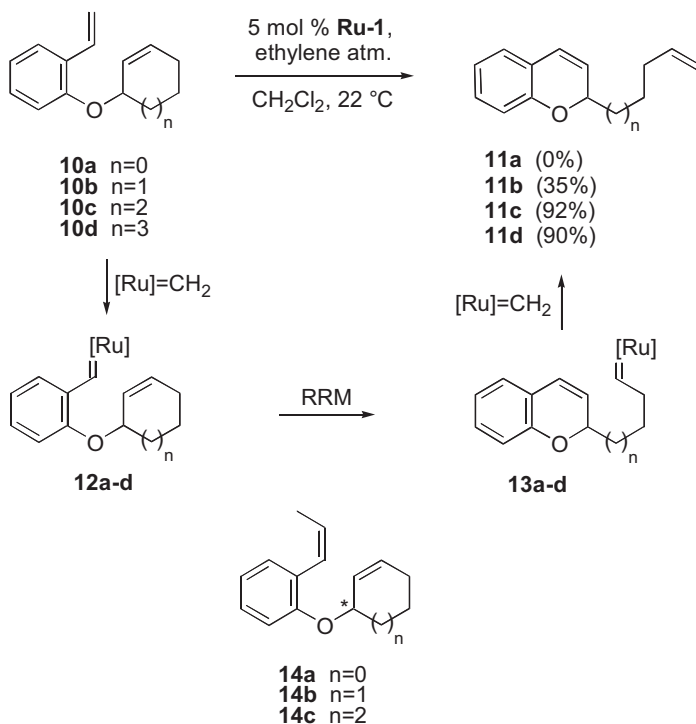
Scheme 2.4.5. Ring-rearrangement metathesis in the total synthesis of alkaloid 251F.

count for the low conversion observed in this case. The subsequent asymmetric total synthesis of the dendrobatid alkaloid 251F underlines the high synthetic utility of such RRM reactions (Scheme 2.4-5) [15].

These examples show that the formation of [3.3.0], [4.3.0], and [5.3.0] bicyclic structures can be readily accomplished *via* RRM of norbornenes. The synthesis of **5b** demonstrates that the preparation of relatively strained [6.3.0] bicycles is feasible, although its scope seems to be generally limited [16].

RRM of alkenyl-substituted cycloolefins is not restricted to strained cycloolefins such as norbornenes; unstrained cycloolefins have also been successfully employed. Hoveyda *et al.* have investigated RRM of styrenes **10** for the preparation of 2-substituted chromenes, a structural motif commonly found in medicinal agents [17]. Semi-empirical calculations had shown that rearranged chromenes **11** are substantially lower in energy than the substrates **10**; thus, product formation should be a favorable process. In initial experiments, cycloheptene **10c** was tested (Scheme 2.4-6). Performing the reaction under an Ar atmosphere, the rearrangement catalyzed by **Ru-1** yielded the desired product **11c** in 44% isolated yield, along with 56% of its metathetic dimer. Conducting the reaction under an ethylene atmosphere afforded **11c** in a 92% yield. The 8-membered analogue **10d** also proved to be a suitable substrate, whereas cyclohexene **10b** afforded **10c** in only low yield and cyclopentene **10a** did not provide any of the ring-rearranged product.

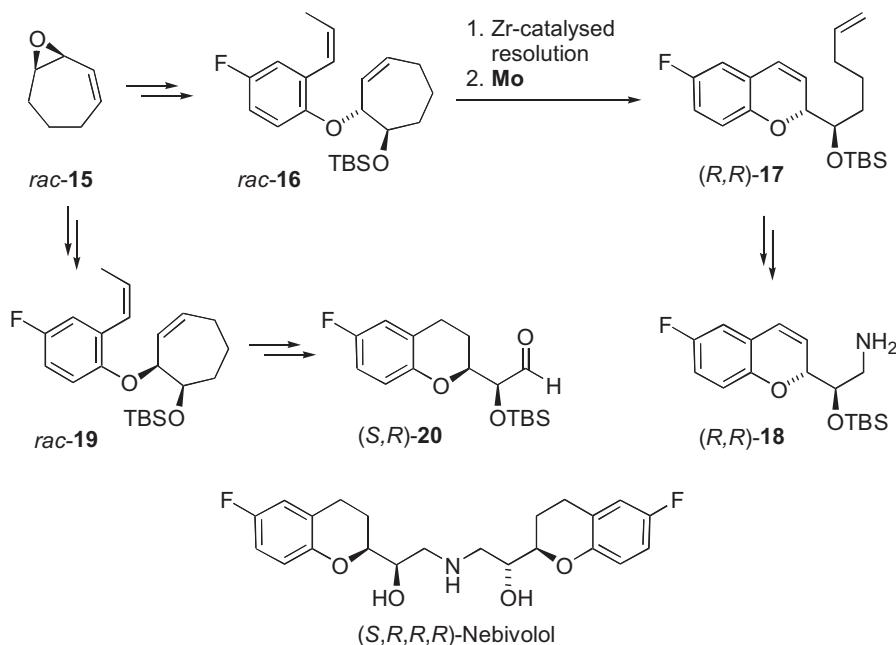
Mechanistic studies suggested that in these reactions the initial metathesis step occurs at the styrene, affording Ru complex **12**, which then attacks the endocyclic



Scheme 2.4-6. Ring-rearrangement reactions of styrenyl ethers **10** and **14**.

double bond to form rearranged **13**, which is finally reacted with another substrate molecule **10** or with ethylene to provide **11** (see also Scheme 2.4-3 and discussion). The failure of cyclopentenyl and cyclohexenyl ethers **10a** and **10b** was ascribed to a kinetic barrier. [2+2]-Cycloaddition of alkylidene **12a,b** would lead to a highly strained tetracyclic intermediate. This mechanism also rationalizes the important role of ethylene. Dimer formation is effectively suppressed in the presence of ethylene since the latter competes with **11** for the alkylidene **13**, thus favoring product formation.

Since metathesis precursors of type **10** were not accessible in enantiopure form, substrates of type **14** with an additional methyl group, which could be obtained in enantiopure form by kinetic resolution of the racemic precursors *via* Zr-mediated ethyl Grignard addition [18], were investigated. In the presence of ethylene, cyclopentene **14a** and cycloheptene **14c** afforded the ring-rearranged **11a** and **11c** in good yields using **Ru-1**. Cyclohexene **14b** did not yield product in substantial amounts. Mechanistic investigations indicated that in the conversions involving disubstituted styrenes, the first attack of the Ru catalyst is likely to occur at the endocyclic double bond. This suggestion is consistent with the successful conversion of cyclopentene **14a** in contrast to monosubstituted styrene **10a**, since the formation of the strained tetracyclic intermediate can be avoided *via* this pathway. The failure of cyclohexene **14b** was again rationalized in terms of kinetic barriers.

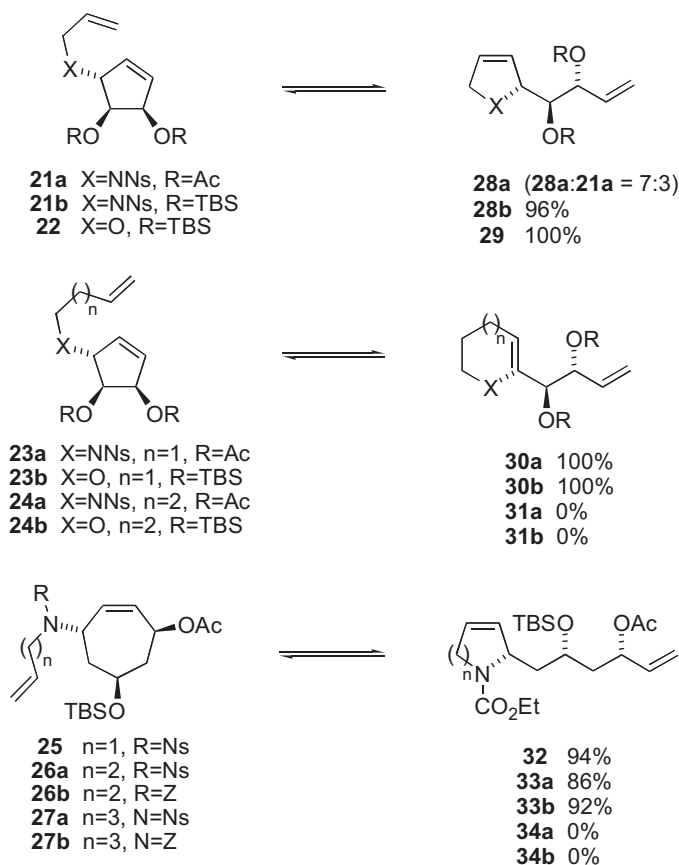


Scheme 2.4-7. Synthesis of (S,R,R,R)-neбиволol.

The concept of Zr-catalyzed resolution and subsequent RRM was applied in the enantioselective synthesis of the anti-hypertensive agent (S,R,R,R)-neбиволol (Scheme 2.4-7) [19]. Both key fragments were prepared in a highly enantioselective manner starting from the same precursor *rac*-15 according to the protocol described above. In the metathesis steps, Schrock's molybdenum catalyst **Mo** was used instead of **Ru-1** since it was found to be more active towards functionalized styrenyl ethers such as **16** or **19**. Coupling of the two fragments **18** and **20** via reductive amination and deprotection afforded neбиволol.

RRM reactions have been advantageously applied in the enantioselective synthesis of heterocycles. These syntheses involve the preparation of a carbocyclic precursor, which is then ring rearranged to the heterocyclic product. This promising concept exploits the fact that asymmetry in the carbocyclic substrate is easily introduced, thereby offering simple and rapid entry into normally more synthetically challenging chiral heterocyclic systems. In the metathesis step, the chirality embedded in the carbocycle is transferred into the product side chain. In collaboration with Van Boom we have investigated the scope of this concept [20]. A number of cyclopentene and cycloheptene derivatives (**21**–**27**) with olefinic side chains of varying lengths have been prepared in enantiomerically pure form and tested in metathesis rearrangement reactions (Scheme 2.4-8).

These examples demonstrate that cyclopentenes and cycloheptenes can be smoothly converted into 5- and 6-membered heterocycles. As the comparison of **21a** and **21b** indicates, bulky substituents in the carbocyclic precursor seem to

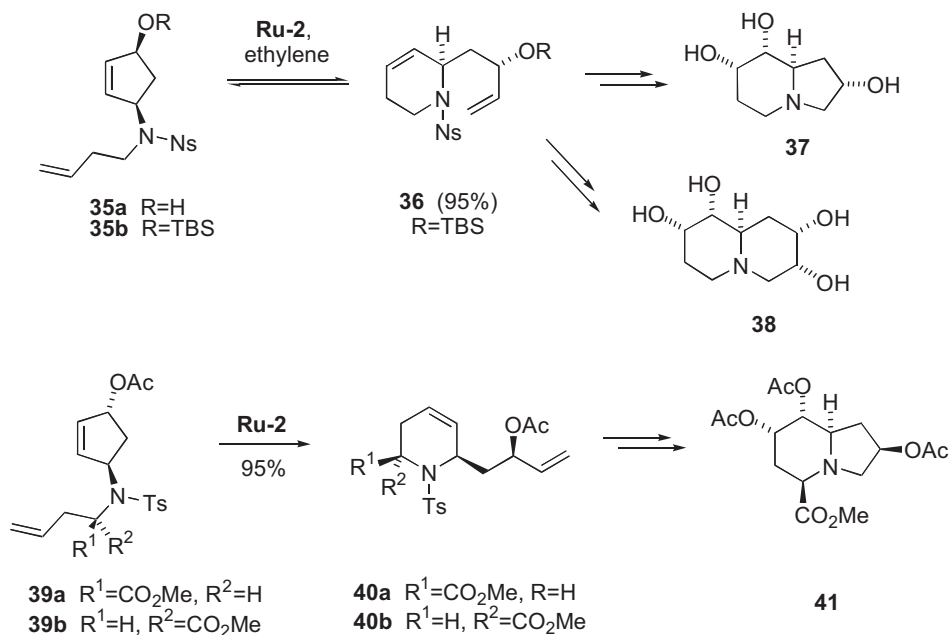


Scheme 2.4-8. RRM of 5- and 7-membered carbocycles.

shift the equilibrium towards the product. The attempted conversion of pentenyl-substituted cyclopentenones **24a,b** or cycloheptenes **27a,b** did not furnish any of the rearranged 7-membered heterocycles. In these cases, the equilibria are obviously on the side of the starting materials. Investigations by Hoveyda *et al.* towards the synthesis of dihydrofurans indicated that the ring rearrangement of cyclohexene derivatives to afford 5-membered heterocycles is also thermodynamically disfavored [21].

We have applied RRM in the stereoselective preparation of the polyhydroxylated indolizidine **37** and quinolizidine **38** starting from **35**, which was easily provided in enantiopure form from 1,4-cyclopentene-*cis*-diol (Scheme 2.4-9) [22]. Whereas the metathesis of **35a** resulted in a mixture of product and starting material in a ratio of 2:1, the use of the bulky TBS-protecting group effected a shift of the equilibrium on the product side; thus, tetrahydropyridine **36** could be virtually quantitatively obtained.

RRM has also been utilized in the stereoselective synthesis of *cis*- and *trans*-2,6-

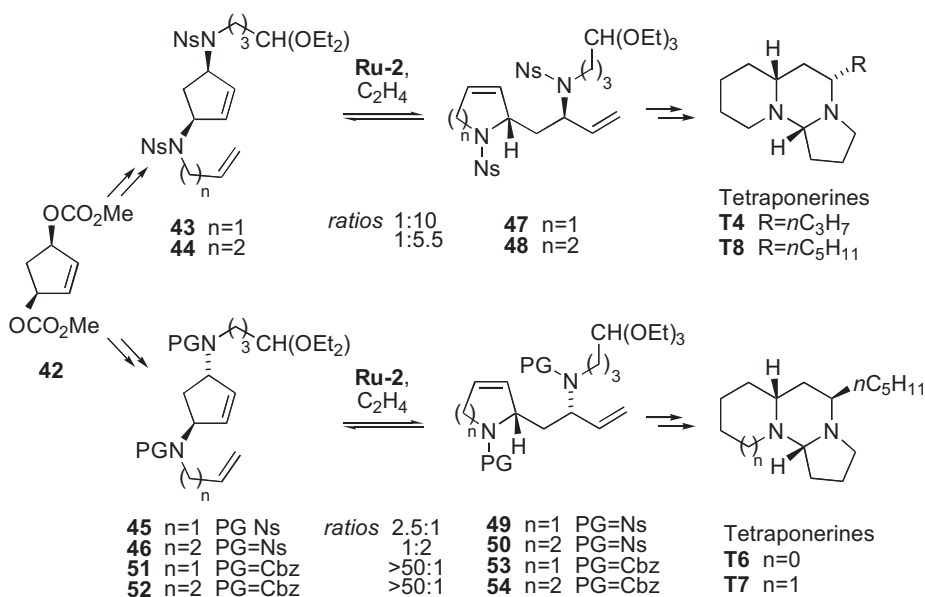


Scheme 2.4-9. Stereoselective synthesis of polyhydroxylated *N*-bicycles via tandem metathesis.

disubstituted piperidines starting from *D*- and *L*-allylglycine derivatives **39a** and **39b** [23]. Under mild metathesis conditions, no racemization of the labile stereocenter adjacent to the methyl ester was observed. The versatility of building blocks of type **40** was demonstrated in the concise synthesis of indolizidine **41**. In this synthesis, racemic allylglycine was used since subsequent epimerization of the mixture of **40a** and **40b** under basic conditions leads exclusively to the thermodynamically more stable 2,6-*cis*-configured piperidine.

We have described a flexible enantioselective approach involving a RRM reaction as the key step towards the tetraoponerines, alkaloids isolated from the venom of the ant *Tetraponera* sp. [24]. Alkenyl-substituted cyclopentenyl amines **43**–**46** giving access to all naturally occurring tetraoponerines **T1**–**T8** were prepared from enantiopure *bis* carbonate **42** (Scheme 2.4-10). RRM of 1,4-*cis*-diamines **43** and **44** afforded mixtures of rearranged products/substrates of >5:1. The reversibility of these reactions could be demonstrated by re-subjecting the rearranged product **48** to the metathesis conditions, which resulted again in the same ratio. When running the reaction under the same conditions with *trans*-diamines **45** and **46**, the equilibrium was far more on the side of the starting materials; however, changing the protecting groups from Ns to Cbz allowed the metathesis reactions to proceed quantitatively. A similar effect of the Cbz-protecting group was observed in the conversions of **26a,b**, indicating that the *N*-protecting group may have a significant influence on the equilibrium.

We have recently successfully applied the concept of ruthenium-catalyzed RRM in a concise synthesis of the indolizidine alkaloid (–)-swainsonine [25]. Hoveyda



Scheme 2.4-10. Ring-rearrangement metathesis in the synthesis of the tetraponerines.

et al. have investigated ring-rearrangement metathesis of allyl cycloalkene ethers of different ring sizes for the preparation of dihydrofurans [21]. RRM for the preparation of cyclic α -trifluoromethyl-substituted α -amino acid esters has also been reported by Osipov and Dixneuf [26].


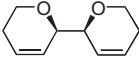
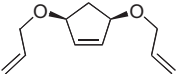
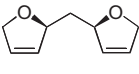
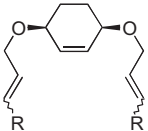
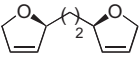
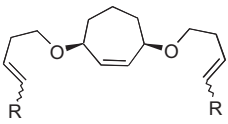
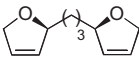
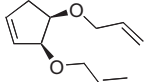
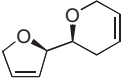
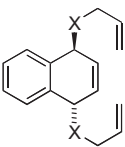
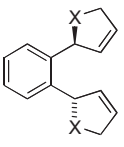
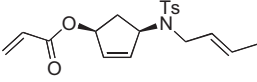
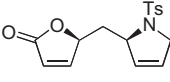
2.4.2.2

RRM of *bis* Alkenyl-Substituted Cycloolefins

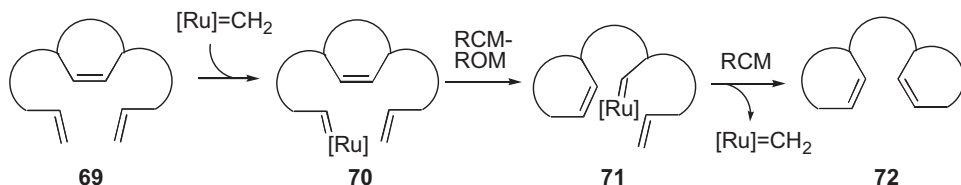
In pioneering work, Grubbs *et al.* have described tandem metathesis reactions of dialkenyl-substituted cycloolefins [27]. Substrates of this type can undergo a sequence of RCM-ROM-RCM to afford bicyclic products. The driving force for this kind of tandem reaction is the entropy gain due to the formation of a volatile olefin, usually ethylene, which is formed as a byproduct. It was demonstrated that cycloolefins of variable ring sizes and alkenyl tether lengths are suitable substrates (Table 2.4-1).

It was found that the 4- and 5-membered cycles were ring opened fastest and gave good to excellent yields, even at relatively high concentrations (entries 1, 2, and 5). Six- (**59a**), 7- (**61a**), and 8-membered (not depicted) substrates yielded mainly oligomeric products and only minor amounts of the desired bicycles at the concentration levels employed for the 4- and 5-membered analogues. Presumably, at higher concentrations, intermolecular ADMET processes were favored. Conducting the reactions at lower concentrations afforded the products in moderate to good yields (entries 3a and 4a). An alternative way to suppress competing oligomerization reactions was to add steric demand to the terminal olefins by additional

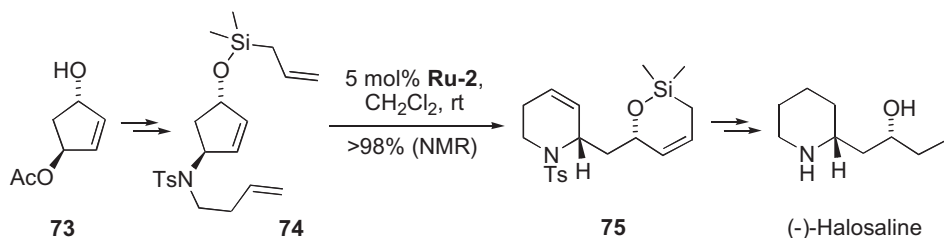
Tab. 2.4-1. RCM-ROM-RCM metathesis reactions.

Entry	Substrate	Product	Yield, Conditions
1	 55	 56	70%, 3 mol% Ru-2 , 0.07 M (C ₆ H ₆), 45 °C, 6 h
2	 57	 58	90%, 5 mol% Ru-2 , 0.1 M (C ₆ H ₆), 60 °C, 2 h
3a R = H 3b R = Me	 59a,b	 60	a: 73%, 3 mol% Ru-2 , 0.008 M (C ₆ H ₆), 45 °C, 6 h b: 42%, 6 mol% Ru-2 , 0.2 M (C ₆ H ₆), 45 °C, 6 h
4a R = H 4b R = Me	 61a,b	 62	a: 57%, 3 mol% Ru-2 , 0.02 M (C ₆ H ₆), 45 °C, 6 h b: 56%, 4 mol% Ru-2 , 0.2 M (C ₆ H ₆), 45 °C, 6 h
5	 63	 64	92%, 5 mol% Ru-2 , 0.04 M (C ₆ H ₆), 60 °C, 3 h
6a R = OCH ₂ 6b R = CO ₂ 6c R = CONMe	 65a,b,c	 66a,b,c	a,b: no product formation c: 95%, 10 mol% Ru-2 , 0.1 M (C ₆ H ₆), 40 °C, 6 h
7	 67	 68	89%, 5 mol% Ru-3 , 0.05 M (CH ₂ Cl ₂), 40 °C, 12 h

substitution (entries 3b and 4b). Such a substitution makes the acyclic olefins less active for intermolecular metathesis, so that intramolecular metathesis reactions are relatively favored. Dimethyl-substituted **59b** and **61b** afforded the bicycles in moderate to good yields, along with only small amounts of oligomeric byproducts at concentrations comparable to those of the 4- and 5-membered analogues. Generally, longer reaction times were needed for these reactions since the rate of conversion was significantly slowed down for these substrates. In the conversions of naphthalene-derived **65a–c**, only amide **65c** afforded product **66c** in good yield,



Scheme 2.4-11. Proposed mechanism for RCM-ROM-RCM.



Scheme 2.4-12. Total synthesis of (–)-halosaline.

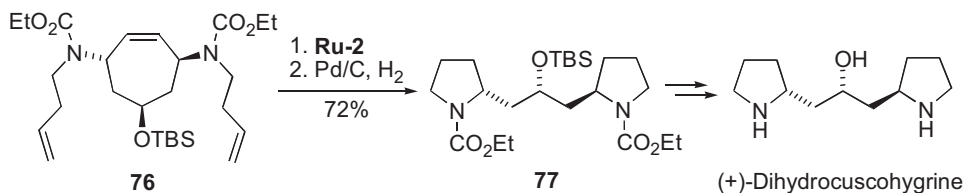
whereas with the ether **65a** and the ester **65b**, none of the desired products of type **66** were detected (entry 6). Probably, with these substrates, the conformations that would be necessary for the ROM-RCM step are energetically challenging. By using the second-generation Grubbs' catalyst **Ru-3**, the substrate scope could be extended [28]. Thus, substrates of type **67** bearing electron-deficient olefins such as α,β -unsaturated carbonyl compounds, which are usually unreactive towards classical Grubbs catalysts **Ru-1** or **Ru-2**, could be successfully converted (entry 7).

There are two conceivable mechanistic rationales consistent with the observed products. The first mechanism involves initial attack towards **69** at the terminal alkene, affording alkylidene **70**, which then attacks the endocyclic double bond to give ring-rearranged **71**. Final RCM then yields the product **72** along with regeneration of the propagating Ru methylenide (Scheme 2.4-11). Alternatively, the sequence might begin with ring opening of the cycloolefin followed by two subsequent RCM reactions (mechanism not depicted).

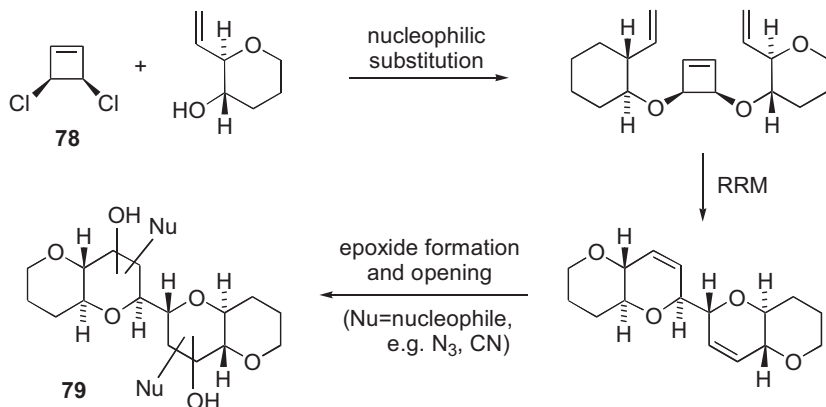
The first mechanism seems more consistent with the observed results, especially with the finding that increased substitution of the tethers in **59** and **61** induced a decrease in the rate of the olefin metathesis. If the reaction started at the endocyclic olefin, little or even no effect would be expected. Nonetheless, the second mechanism cannot be completely ruled out, especially for substrates with notable ring strain.

We have employed a domino RCM-ROM-RCM reaction in the synthesis of the piperidine alkaloid (–)-halosaline (Scheme 2.4-12) [29]. Metathesis precursor **74** was readily prepared starting from acetate **73**. The subsequent metathesis reaction proceeded smoothly in virtually quantitative yield to afford bicyclic **75**, which was converted into (–)-halosaline in three steps.

A similar RRM reaction was employed as the key step in the synthesis of the alkaloid (–)-indolizidine 167B [30].



Scheme 2.4-13. RRM as the key step in the synthesis of (+)-dihydrocuscohygrine.



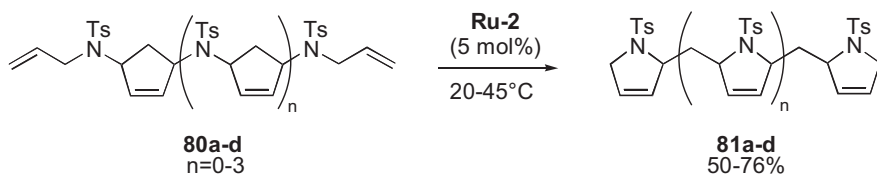
Scheme 2.4-14. RRM as the key step in the preparation of polyether-type structures.

We have reported the first enantioselective synthesis of (+)-dihydrocuscohygrine *via* tandem metathesis (Scheme 2.4-13) [31]. Cycloheptene **76** was prepared in enantiomerically pure form from tropone. The RRM reaction proceeded quantitatively (determined by $^1\text{H-NMR}$); however, upon concentration of the crude reaction mixture, decomposition of the newly formed product was observed, presumably induced by the ruthenium residues in the solution. Therefore, the crude product was hydrogenated in one pot affording **77** in 72% yield. Cleavage of the *N*- and *O*-protecting groups and protonation afforded (+)-dihydrocuscohygrine hydrochloride.

A similar strategy has been employed in the enantioselective synthesis of the bis-piperidine alkaloid (–)-anaferine [32].

Recently, Nicolaou *et al.* realized the potential of cyclobutene **78** as a template on which useful chiral tandem metathesis substrates can be built (Scheme 2.4-14). This was the key concept in the preparation of cyclic polyether-type structures **79**, a structural motif that frequently occurs in natural products, e.g., in marine neurotoxins [33].

Burke *et al.* have reported a significantly simplified access to a precursor of the polyether macrolide halichondrin B *via* this methodology [34]. Schreiber *et al.* have employed an RCM-ROM-RCM reaction of a dialkenyl-substituted norbornene as a complexity-generating reaction in “diversity-oriented organic synthesis” [35, 36].



Scheme 2.4-15. Domino sequences of diamino-substituted polycyclopentenenes.

2.4.2.3

Tandem Reactions of Polycycloolefins

RRM reactions were successfully extended to polycyclic precursors by Grubbs *et al.* [37]. Treatment of *N*-protected polyamines **80a–d** bearing one to four cycloolefins with catalytic amounts of **Ru-2** resulted in the formation of *N*-protected polycyclic amines **81a–d** (Scheme 2.4-15). The mechanism is thought to be analogous to the mechanism outlined in Scheme 2.4-11. In these reactions, the cycloolefins can be considered as “relays,” which transfer the Ru alkylidene intramolecularly from one double bond to another. The polycyclization reactions of substrates **80a** and **80b** containing one or two cyclopentene moieties were found to proceed in good yields. For the successful conversion of the analogous **80c** and **80d** with an increased number of cyclopentene relays, lower concentrations and reaction temperatures had to be employed in order to efficiently suppress intermolecular side reactions. However, this in no way detracts from the impressive nature of these transformations.

2.4.3

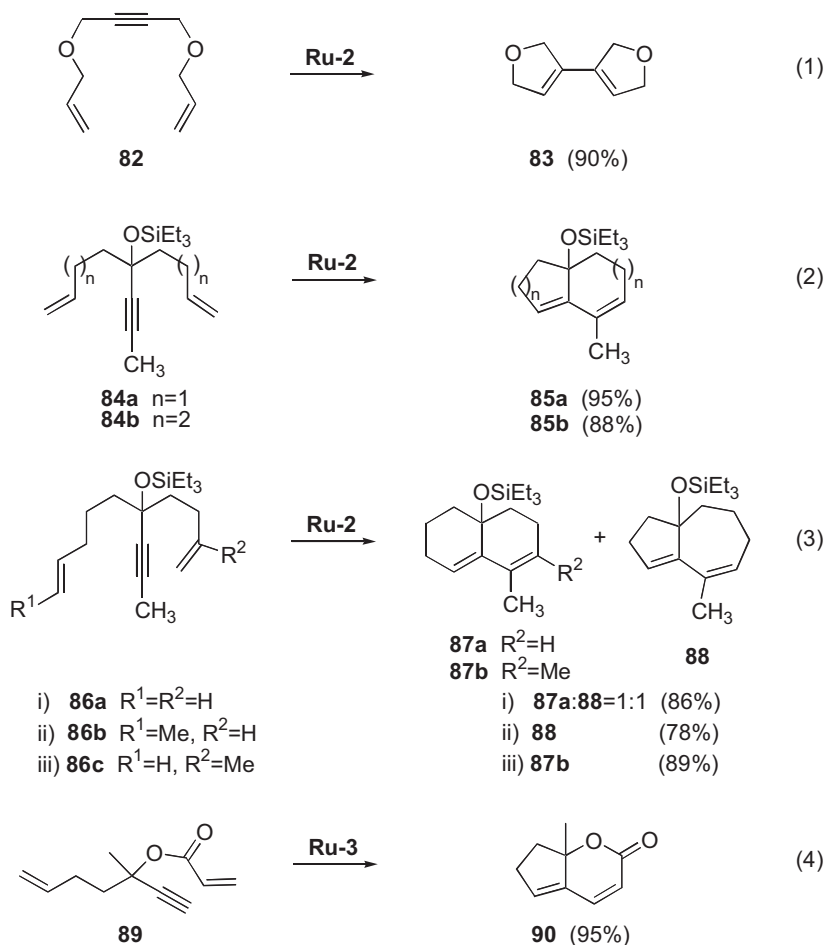
Tandem RCM Involving Enyne Reactions

In enyne metathesis reactions, an alkyne reacts with a metal carbene to afford a vinylidene carbene, which can undergo further intra- or intermolecular reactions. As a cycloolefin, an alkyne can thus act as a “relay” in domino metathesis reactions (compare Chapter X.2.3). Several intra- and intermolecular domino reactions involving enyne metathesis steps have been described for the preparation of monocyclic and oligocyclic systems.

2.4.3.1

Tandem Reactions with Triple Bonds As “Relays”

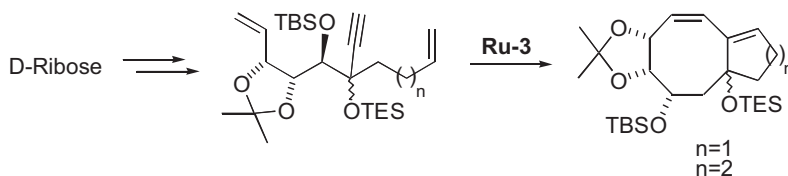
Tandem reactions involving enyne metathesis were first reported by Grubbs *et al.* [38]. In initial studies, dienyne **82** could efficiently be converted to bicycle **83** using **Ru-2** as the catalyst (Scheme 2.4-16, Eq. (1)). If the intervening alkyne is placed in a branched position between the olefins, the cyclization leads to fused ring systems (Scheme 2.4-16, Eqs. (2–4)). Those highly efficient tandem processes, in which two rings and two C–C bonds are formed in a single step, give yields generally higher



Scheme 2.4-16. Tandem metathesis reactions of dienynes.

than 75%. Mechanistically, the initial attack of the catalyst in these transformations was proposed to occur at one of the olefins, followed by a ring-closing metathesis reaction with the alkyne moiety and subsequent RCM. The alkyne can be considered as a relay between the two olefins.

Substrate **84a** readily afforded [4.3.0]-bicycle **85a**. This example shows that enyne metathesis is highly favored over competing RCM of the olefin moieties, which would afford a 7-membered ring. The RCM-product was formed in only trace amounts of less than 3%. Bis-homologous dienyne **84b** is easily cyclized to the corresponding [5.4.0] bicyclic ring system **85b**. When the unsymmetrical diene **86a** was treated with **Ru-2** catalyst, two bicyclic compounds, **87a** and **88**, were isolated in equal amounts. The statistical formation of these bicycles is probably due to unselective attack of the Ru catalyst in the initial acyclic metathesis. Control of the initial step could be achieved by different substitution patterns on the olefins.



Scheme 2.4-17. Dienyne metathesis of carbohydrate-derived substrates.

Thus, substrates **86b** and **86c** afforded only one product (**88** and **87b**, respectively). The regioselectivity can be explained by preferential initial attack of the catalyst at the monosubstituted double bond. Furthermore, the synthesis of **87b** proves that even tetrasubstituted double bonds can be formed. This regiochemical control not only provides additional evidence for the proposed mechanism but also widens the scope of this tandem reaction significantly. By using the second-generation Grubbs' catalyst **Ru-3**, substrates involving an electron-deficient olefin such as acrylic ester **89** could also be successfully converted [28]. The formation of the product is rationalized *via* initial attack of the methylidene species at the more electron-rich, alkyl-substituted olefin.

Hanna *et al.* have described the preparation of various highly functionalized [6.4.0] and [6.3.0] bicyclic ring systems utilizing tandem RCM of dienyne starting from carbohydrates (Scheme 2.4-17) [39–41].

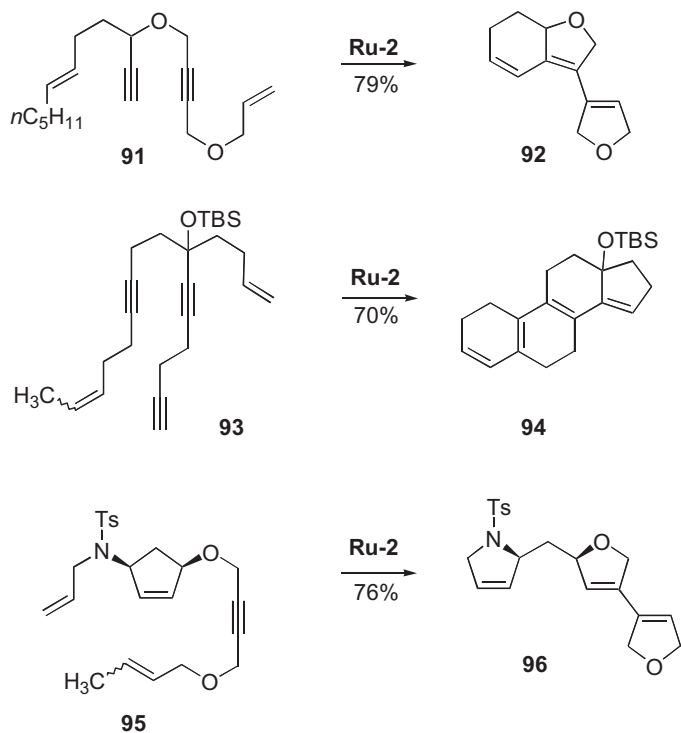
Grubbs *et al.* have extended this concept to the synthesis of polycyclic structures (Scheme 2.4-18) [37]. Acyclic dienes **91** and **93** with various numbers of acetylenic relay units were converted to polycycles **92** and **94** in good yields. The reaction is postulated to start at the monosubstituted olefin, followed by a series of intramolecular ring-closing enyne metatheses and finally terminated by a RCM step. The synthesis of **94** illustrates the formation of a polycycle with a steroid backbone with all four rings being formed in one step. The conversion of **95** into **96** is an example of both an alkyne and a cyclic olefin acting as relays in such a cascade reaction.

2.4.3.2

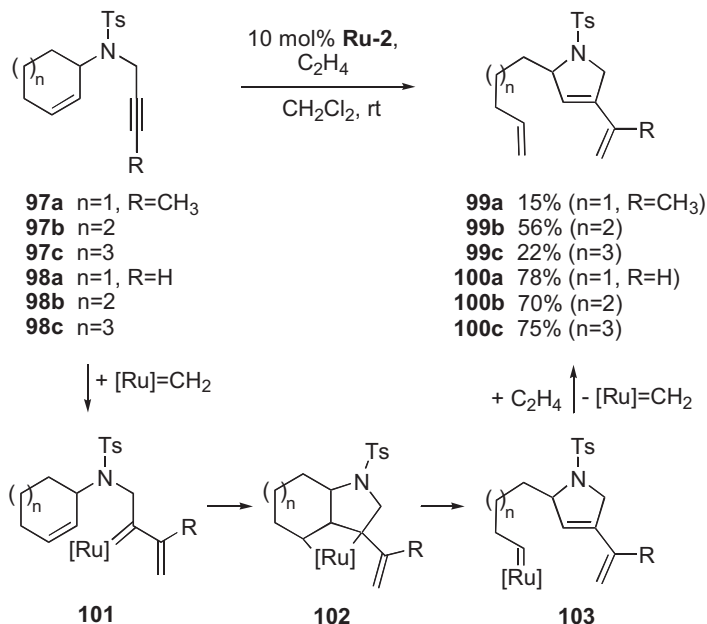
Tandem Processes Involving Ring Rearrangement

Mori *et al.* have described atom-economical domino reactions of alkynyl-substituted cycloolefins [42]. In the presence of ethylene, substrates **97** and **98** underwent ring rearrangement to afford enedienes **99** and **100**, respectively (Scheme 2.4-19). In this transformation, one methylidene part of the ethylene is formally transferred to the alkyne and the other to the alkene moiety. In contrast to rearrangement reactions of alkenyl-substituted cycloolefins (Chapter X.2.1), which represent equilibrium reactions, in these transformations product formation is strongly facilitated due to the formation of an 1,3-butadiene moiety, which is relatively unreactive towards the metathesis catalyst.

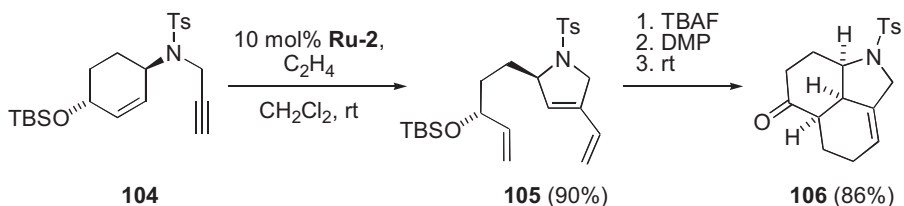
The reaction is assumed to start with an intermolecular enyne metathesis between the alkyne moiety and the propagating ruthenium methylidene complex. Resulting vinylidene complex **101** then attacks the endocyclic double bond to



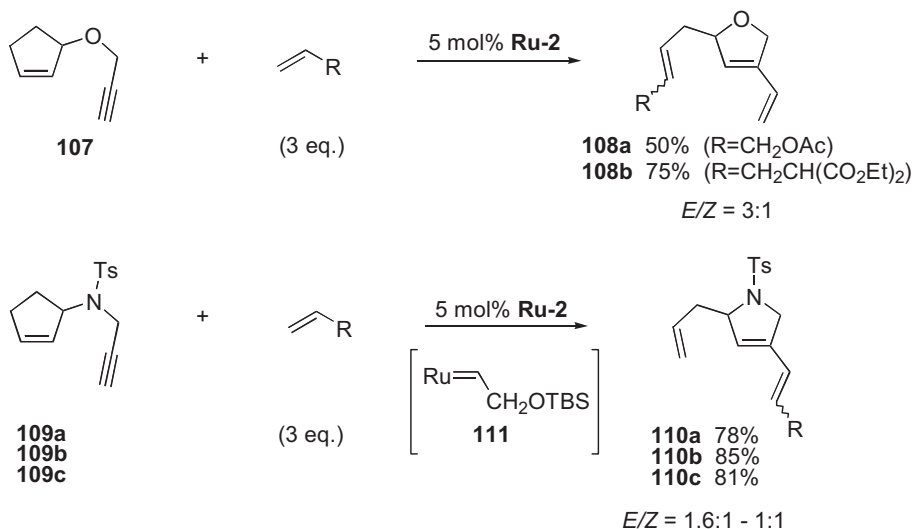
Scheme 2.4-18. Domino metathesis reactions of enynes.



Scheme 2.4-19. Ring-rearrangement reactions of alkynyl-substituted cycloolefins **97** and **98**.



Scheme 2.4-20. Synthesis of tricycle **106** via ring rearrangement and Diels-Alder reaction.

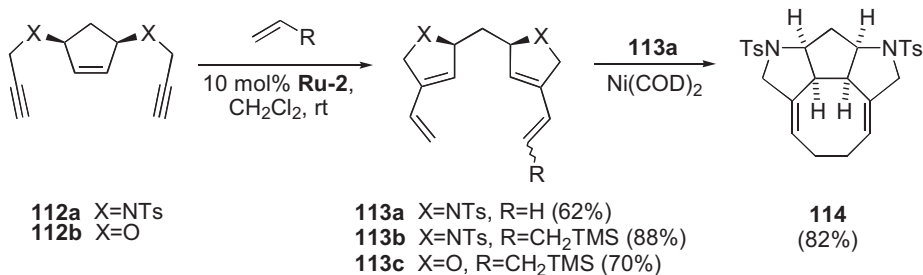


Scheme 2.4-21. Rearrangement reactions of **107** and **109**.

afford metallacyclobutane **102**. [2+2]-Cycloreversion gives the ring-rearranged intermediate **103**, which undergoes CM with ethylene, yielding products **99** and **100**. Higher yields obtained with monosubstituted alkynes **98** compared with their methyl-substituted analogues **97** were ascribed to a facilitated formation of intermediate **102** due to attenuated steric strain. The addition of an external olefin is crucial in these rearrangement reactions. In its absence, polymerization would occur by reaction of alkylidene **103** with another molecule of **97** or **98**.

The versatility of such a domino process was demonstrated by the conversion of TBS-ether **104** (Scheme 2.4-20). After ring rearrangement, cleavage of the silyl ether, and oxidation of the free hydroxy group, a Diels-Alder reaction spontaneously occurred to afford tricyclic **106** in only four steps starting from monocyclic **104**.

We have studied similar rearrangement reactions utilizing olefins other than ethylene as the CM partner (Scheme 2.4-21) [43]. Surprisingly, depending on the heteroatom in the propargylic position, different types of product were obtained. Whereas cyclopentenol-derived **107** yielded dihydrofurans of general type **108** upon rearrangement, propargylic amine **109** afforded products of type **110**, in which the alkylidene part of the added olefin was incorporated in the butadiene moiety.



Scheme 2.4-22. Domino reactions of *bis*-alkynyl-substituted cycloolefins **112a,b**.

This finding was rationalized in terms of different reaction mechanisms. Whereas **107** is presumed to be attacked first by Ru methylidene as outlined in Scheme 2.4-19 (with the reaction sequence being terminated by CM with the added olefin), with **109** initial attack is assumed to be effected by ruthenium alkylidene **111**. An enhanced reactivity of the alkyne moiety of the propargylic amines compared with the propargylic ethers might be deduced from this finding. While substrates of type **109** react immediately with **111** [44], **107** reacts only with the Ru methylidene species, which is slower to form.

When dialkynyl-substituted cycloalkenes are used as the substrates, a second cyclization can take place to provide bicyclic *bis*-butadienes. Thus, **112a** and **112b** afforded bicyclic **113a–c** in moderate to good yields in the presence of an added olefin (Scheme 2.4-22). Butadiene **113a** was further functionalized by a diastereoselective Ni-catalyzed [4+4]-cycloaddition.

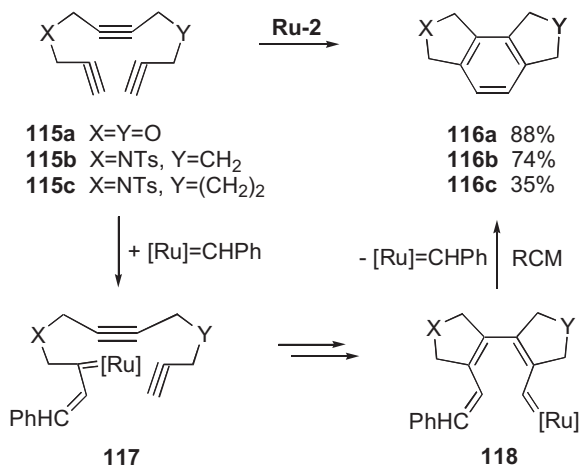
North *et al.* have reported domino metathesis reactions of *bis*-alkynyl-substituted norbornenes [45]. The *bis*-butadiene products were subsequently functionalized by double Diels-Alder reactions in a highly diastereoselective manner with various dienophiles.

Ring-rearrangement reactions of alkynyl-substituted cycloolefins have also been reported using non-metathesis catalysts to afford products that formally result from a metathesis reaction. These transformations do not proceed *via* a Chauvin mechanism, and in the literature they are discussed as both “enyne metathesis reactions” and “skeletal rearrangements”. For these transformations, Pd [46], Ru [47], Pt [48], and Ga [49] catalysts have proved to be effective [50].

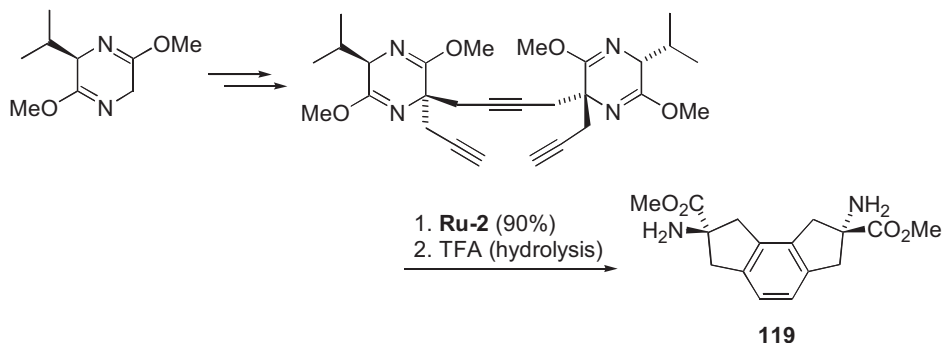
2.4.3.3

Alkyne Trimerizations Catalyzed by Metathesis Catalysts

We have found ruthenium complex **Ru-2** to catalyze the isomerization of triynes **115** to benzenes [51]. Benzene derivatives with two annelated 5-membered rings such as **116a** and **116b** were formed in good yields (Scheme 2.4-23). Substrates with longer tethers (four or five atoms) between the alkyne moieties (such as **115c**) resulted mainly in polymeric products by undesired intermolecular reactions. The proposed catalytic cycle starts with initial attack of the Ru benzylidene to one of the terminal triple bonds to give **117**. By a cascade of two consecutive intramolecular



Scheme 2.4-23. Aromatization of triynes.



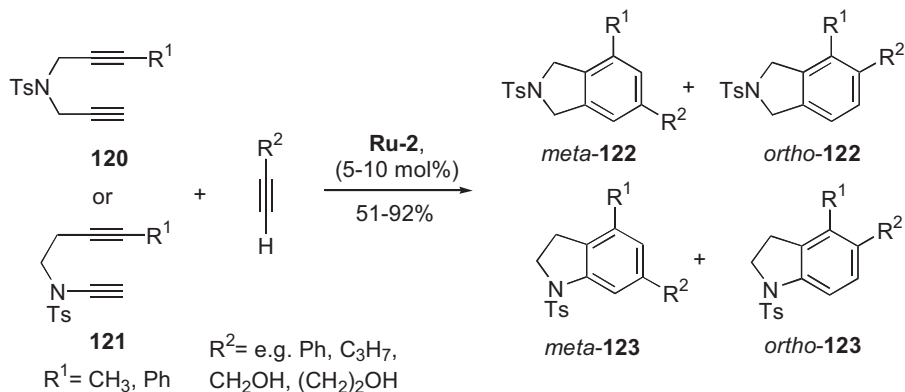
Scheme 2.4-24. Ru-catalyzed alkyne trimerization for the preparation of amino acid derivatives.

enyne metatheses and a final RCM step, the aromatic product **116** is formed, along with regeneration of the propagating Ru benzylidene. The reaction is thermodynamically strongly favored by the formation of an aromatic system.

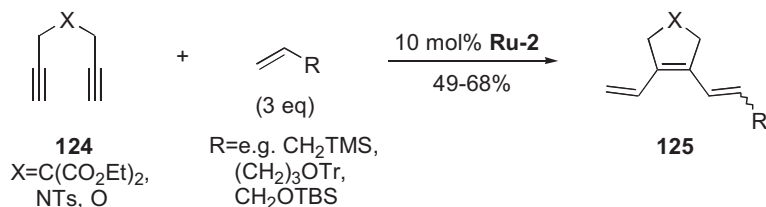
This concept has recently been employed by Undheim *et al.* in the preparation of rigid C₂-symmetrical *as*-indacene-bridged *bis*(α -amino acid) derivatives **119** (Scheme 2.4-24) [52].

An intermolecular variant has been reported by Witulski *et al.* [53]. In the presence of an external alkyne, monosubstituted 1,6-diynes **120** and **121** afford isoindolines **122** and indolines **123** in moderate to good yields (Scheme 2.4-25). The *meta*-products are formed preferentially with ratios of *meta/ortho* >5:1. The high regioselectivity can be explained in terms of initial attack of the catalyst on the less sterically hindered, monosubstituted triple bond in **120** and **121**.

Wilkinson's catalyst [RhCl(PPh₃)₃] also turned out to be a suitable catalyst for these conversions, affording the products predominantly with reversed regiochemistry.



Scheme 2.4-25. Cycloadditions of diynes **120** and **121** with terminal alkynes.



Scheme 2.4-26. Cyclization of 1,6-diynes in the presence of terminal olefins.

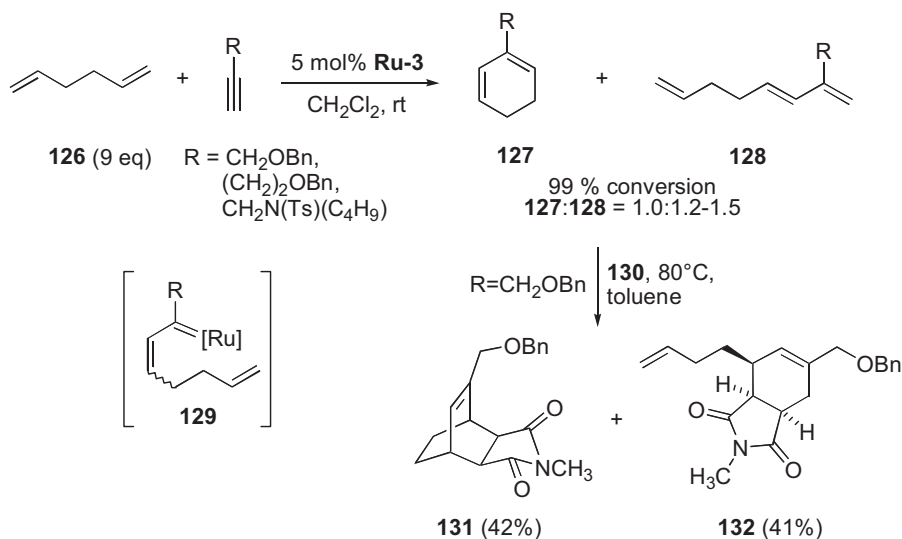
A three-component intermolecular variant of alkyne trimerization has been reported by Roy *et al.* [54]. Various propargylic ethers and esters could be trimerized efficiently using **Ru-2**. The formation of the 1,2,4-trisubstituted benzene isomers was strongly favored over the 1,3,5-isomers; ratios of 3:1 to 20:1 were found.

These accomplishments demonstrate that the Grubbs catalyst is also a suitable catalyst for alkyne trimerizations and in some cases is a versatile alternative for other metals classically used in these transformations, such as Co [55] and Rh [56, 57].

2.4.3.4

Other Tandem Processes Involving C–C Triple Bonds

In the presence of an added olefin, 1,6-diynes **124** are cyclized in an atom-economical reaction, affording products of general type **125** (Scheme 2.4-26) [58]. Several terminal olefins could be employed as the CM partners in this tandem reaction, and *E/Z* selectivity was generally low (1.5:1–1:1). High selectivity was found only with sterically demanding olefins such as TBS-protected allyl alcohol ($\text{R} = \text{CH}_2\text{OTBS}$, *E/Z* = 5:1). Strikingly, in all cases only traces of the alkene homodimer were detected, thus demonstrating the remarkable chemoselectivity of these transformations.



Scheme 2.4-27. Tandem sequence of enyne metathesis/RCM.

Substrates with a longer tether between the two alkyne moieties (1,7- and 1,8-diynes), which would afford 6- or 7-membered rings, did not react, and substrates in which one of the alkynes was disubstituted also proved unsuitable.

Diver *et al.* have described a tandem metathesis process involving an enyne metathesis and a subsequent RCM [59]. 1,5-Hexadiene (**126**) and a variety of terminal alkynes were thus converted into 2-substituted 1,3-cyclohexadienes **127** (Scheme 2.4-27). The second-generation Grubbs' catalyst **Ru-3** gave the best yields, while **Ru-2** afforded the products in only trace amounts. Disubstituted alkynes gave substantially lower yields.

An inherent problem of this concept is that only the *cis*-configured alkylidene **129** formed in the initial enyne step can undergo cyclization. The ratio of *cis/trans* products, however, is low (1:1 to 1:2) and could not be improved significantly by varying the catalyst, reaction temperature, or solvent, which means that at least 50% of the alkyne is converted into undesired **128**. After the metathesis reaction, the crude product of the reaction of **126** with propargyl benzyl ether was shown to react quantitatively with *N*-methylmaleimide (**130**) in a Diels-Alder reaction affording tricyclic **131** along with byproduct **132**. Despite the moderate yield of 42%, this sequence also exemplifies the fact that by using tandem processes, complex structures can be quickly prepared starting from relatively simple substrates.

2.4.4

Summary and Outlook

The aforementioned examples bear testament to the utility of catalytic olefin metathesis in tandem reactions. Recent advances in catalyst technology now allow

multi-C–C bond-forming–bond breaking reactions, which were previously unimaginable, with products (often chiral) of impressive complexity available from simple starting materials. Given the advantages of tandem metathesis reactions in terms of atom economy and catalytic efficiency, we can only expect the recent surge of interest in these processes to grow further.

References

- See for example: (a) F. LYNEN, *Pure Appl. Chem.* **1967**, *14*, 137–167. (b) R. B. HERBERT, *Nat. Prod. Rep.* **1991**, *8*, 185–209. (c) E. LEETE, *Planta Med.* **1990**, *56*, 339–352. (d) E. J. COREY, W. E. RUSSEY, P. R. ORTIZ DE MOTELLA, *J. Am. Chem. Soc.* **1966**, *88*, 4750–4751. (e) E. E. VAN TAMELEN, J. D. WILLET, R. B. CLAYTON, K. E. LORD, *J. Am. Chem. Soc.* **1966**, *88*, 4752–4754. (f) E. E. VAN TAMELEN, *J. Am. Chem. Soc.* **1982**, *104*, 6480–6481. (g) E. J. COREY, S. C. VIRGIL, *J. Am. Chem. Soc.* **1991**, *113*, 4025–4026. (h) E. J. COREY, S. C. VIRGIL, S. SARSHAR, *J. Am. Chem. Soc.* **1991**, *113*, 8171–8172. (i) E. J. COREY, S. C. VIRGIL, D. R. LIU, S. SARSHAR, *J. Am. Chem. Soc.* **1992**, *114*, 1524–1525. (j) E. J. COREY, S. C. VIRGIL, H. CHENG, C. H. BAKER, S. P. T. MATSUDA, V. SINGH, S. SARSHAR, *J. Am. Chem. Soc.* **1995**, *117*, 11819–11820.
- For recent reviews on domino reactions, see: (a) L. F. TIETZE, *Chem. Rev.* **1996**, *96*, 115–136. (b) H. WALDMANN, *Domino Reactions in Organic Synthesis Highlights II*, H. WALDMANN (Ed.), VCH, Weinheim, 1995, pp. 193–202. (c) L. F. TIETZE, U. BEIFUSS, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163. (d) T. L. HO, *Tandem Organic Reactions*, Wiley, New York, **1992**.
- (a) M. MORENO-MANAS, R. PLEIXATS, A. SANTAMARIA, *Synlett* **2001**, 1784–1786. (b) D. BENTZ, S. LASCHAT, *Synthesis* **2000**, 1766–1773. (c) D. A. HEERING, D. T. TAKATA, C. KWON, W. F. HUFFMAN, J. SAMANEN, *Tetrahedron Lett.* **1998**, *39*, 6815–6818.
- (a) R. GRIGG, M. YORK, *Tetrahedron Lett.* **2000**, *41*, 7255–7258. (b) P. EVANS, R. GRIGG, M. I. RAMZAN, V. SRIDHARAN, M. YORK, *Tetrahedron Lett.* **1999**, *40*, 3021–3024. (c) R. GRIGG, V. SRIDHARAN, M. YORK, *Tetrahedron Lett.* **1998**, *39*, 4139–4142.
- (a) A. G. M. BARRETT, M. AHMED, S. P. BAKER, S. P. D. BAUGH, D. C. BRADDOCK, P. A. PROCOPIOU, A. J. P. WHITE, D. J. WILLIAMS, *J. Org. Chem.* **2000**, *65*, 3716–3721. (b) S. D. BURKE, R. A. NG, J. A. MORRISON, M. J. ALBERTI, *J. Org. Chem.* **1998**, *63*, 3160–3161. (c) J. LIMANTO, M. L. SNAPPER, *J. Am. Chem. Soc.* **2000**, *122*, 8071–8072.
- (a) G. S. WEATHERHEAD, J. G. FORD, E. J. ALEXANIAN, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2000**, *122*, 1828–1829. (b) D. R. CEFALO, A. F. KIELY, M. WUCHRER, J. Y. JAMIESON, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2001**, *123*, 3139–3140. (c) X. TENG, D. R. CEFALO, R. R. SCHROCK, A. H. HOVEYDA, *J. Am. Chem. Soc.* **2002**, *124*, 10779–10784.
- For double RCM, see for example: (a) C. BAYLON, M.-P. HECK, C. MIOSKOWSKI, *J. Org. Chem.* **1999**, *64*, 3354–3360. (b) M. LAUTENS, G. HUGHES, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 129–131. (c) J. S. CLARK, O. HAMELIN, *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 372–374. (d) M. J. BASSINDALE, A. S. EDWARDS, P. HAMLEY, H. ADAMS, J. P. A. HARRITY, *Chem. Commun.* **2000**, 1035–1036. (e) B. SCHMIDT, H. WILDEMANN, *J. Org. Chem.* **2000**, *65*, 5817–5822. (f) D. J. WALLACE, J. M. GOODMAN, D. J. KENNEDY, A. J. DAVIES, C. J. COWDEN, M. S. ASHWOOD, I. F. COTRELL, U.-H. DOLLING, P. J. REIDER, *Org. Lett.* **2001**, *3*, 671–674. (g) S. MA, B. NI, *Org. Lett.* **2002**, *4*, 639–641.

- 8 For a triple RCM, see: M.-P. HECK, C. BAYLON, S. P. NOLAN, C. MIOSKOWSKI, *Org. Lett.* **2001**, 3, 1989–1991.
- 9 Polyolefins have been shown to undergo quantitative ring-closing metathesis: G. W. COATES, R. H. GRUBBS, *J. Am. Chem. Soc.* **1996**, 118, 229–230.
- 10 R. STRAGIES, S. BLECHERT, *Synlett* **1998**, 169–170.
- 11 For similar RRM of norbornenes, see: H. HAGIWARA, T. KATSUMI, S. ENDOU, T. HOSHI, T. SUZUKI, *Tetrahedron* **2002**, 58, 6651–6654.
- 12 PLUMET et al. have described RRM of 2-alkenyl and alkynyl substituted 7-oxanorborn-5-enes: (a) O. ARJONA, A. G. CSÁKY, M. C. MURCIA, J. PLUMET, *Tetrahedron Lett.* **2000**, 41, 9777–9779. (b) O. ARJONA, A. G. CSÁKY, M. C. MURCIA, J. PLUMET, *ARKIVOC* **2002**, 5, 171–180.
- 13 O. ARJONA, A. G. CSÁKY, R. MEDEL, J. PLUMET, *J. Org. Chem.* **2002**, 67, 1380–1383.
- 14 J. HUANG, E. D. STEVENS, S. P. NOLAN, J. L. PETERSON, *J. Am. Chem. Soc.* **1999**, 121, 2674–2678. (b) J. HUANG, H.-J. SCHANZ, E. D. STEVENS, S. P. NOLAN, *Organometallics* **1999**, 18, 5375–5380.
- 15 A. WROBLESKI, K. SAHASRABUDHE, J. AUBÉ, *J. Am. Chem. Soc.* **2002**, 124, 9974–9975.
- 16 PHILIPS et al. have described RRM reactions of bicyclo[2.2.2]octenes: T. L. MINGER, A. J. PHILIPS, *Tetrahedron Lett.* **2002**, 43, 5357–5359.
- 17 (a) J. P. A. HARRITY, M. S. VISSER, J. D. GLEASON, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1997**, 119, 1488–1489. (b) J. P. A. HARRITY, D. S. LA, D. R. CEFALO, M. S. VISSER, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1998**, 120, 2343–2351.
- 18 (a) J. P. MORKEN, M. T. DIDIUK, M. S. VISSER, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1994**, 116, 3123–3124. (b) M. S. VISSER, N. M. HERON, M. T. DIDIUK, J. F. SAGAL, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1996**, 118, 4291–4298. (c) M. S. VISSER, J. P. A. HARRITY, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1996**, 118, 3779–3780.
- 19 C. W. JOHANNES, M. S. VISSER, G. S. WEATHERHEAD, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1998**, 120, 8340–8347.
- 20 (a) H. OVAA, C. STAPPER, G. A. VAN DER MAREL, H. S. OVERKLEEF, J. H. VAN BOOM, S. BLECHERT, *Tetrahedron* **2002**, 58, 7503–7518. (b) H. OVAA, R. STRAGIES, G. A. VAN DER MAREL, J. H. VAN BOOM, S. BLECHERT, *Chem. Commun.* **2000**, 1501–1502.
- 21 J. A. ADAMS, J. G. FORD, P. J. STAMATOS, A. H. HOVEYDA, *J. Org. Chem.* **1999**, 64, 9690–9696.
- 22 U. VOIGTMANN, S. BLECHERT, *Org. Lett.* **2000**, 2, 3971–3974.
- 23 U. VOIGTMANN, S. BLECHERT, *Synthesis* **2000**, 893–898.
- 24 R. STRAGIES, S. BLECHERT, *J. Am. Chem. Soc.* **2000**, 122, 9584–9591.
- 25 N. BUSCHMANN, A. RÜCKERT, S. BLECHERT, *J. Org. Chem.* **2002**, 67, 4325–4329.
- 26 S. N. OSIPOV, N. M. KOBELÍKOVA, G. T. SHCHETNIKOV, A. F. KOLOMIETS, C. BRUNEAU, P. H. DIXNEUF, *Synlett* **2001**, 621–622.
- 27 W. J. ZUERCHER, M. HASHIMOTO, R. H. GRUBBS, *J. Am. Chem. Soc.* **1996**, 118, 6634–6640.
- 28 T.-L. CHOI, R. H. GRUBBS, *Chem. Commun.* **2001**, 2648–2649.
- 29 R. STRAGIES, S. BLECHERT, *Tetrahedron* **1999**, 55, 8179–8188.
- 30 J. ZAMINER, C. STAPPER, S. BLECHERT, *Tetrahedron Lett.* **2002**, 43, 6739–6741.
- 31 C. STAPPER, S. BLECHERT, *J. Org. Chem.* **2002**, 67, 6456–6460.
- 32 S. BLECHERT, C. STAPPER, *Eur. J. Org. Chem.* **2002**, 2855–2858.
- 33 K. C. NICOLAOU, J. A. VEGA, G. VASSILIKOGIANNAKIS, *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 4441–4445.
- 34 S. D. BURKE, K. J. QUINN, V. J. CHEN, *J. Org. Chem.* **1998**, 63, 8626–8627.
- 35 (a) D. LEE, J. K. SELLO, S. L. SCHREIBER, *Org. Lett.* **2000**, 2, 709–712. (b) S. L. SCHREIBER, *Science* **2000**, 287, 1964–1969.
- 36 For another example of RCM-ROM-RCM, see: G. MEHTA, J. NANDAKUMAR, *Tetrahedron Lett.* **2002**, 43, 699–702.
- 37 W. J. ZUERCHER, M. SCHOLL, R. H. GRUBBS, *J. Org. Chem.* **1998**, 63, 4291–4298.

- 38 S.-H. KIM, N. BOWDEN, R. H. GRUBBS, *J. Am. Chem. Soc.* **1994**, *116*, 10801–10802.
- 39 F.-D. BOYER, I. HANNA, L. RICARD, *Org. Lett.* **2001**, *3*, 3095–3098.
- 40 For further examples of tandem diyne metathesis, see: (a) E. M. CODESIDO, L. CASTEDO, J. R. GRANJA, *Org. Lett.* **2001**, *3*, 1483–1486.
(b) J. HUANG, H. XIONG, R. P. HSUNG, C. RAMESHKUMAR, J. A. MULDER, T. P. GREBE, *Org. Lett.* **2002**, *4*, 2417–2420. (c) J. EFSKIND, C. RÖMMING, K. UNDHEIM, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697–2703.
(d) K. UNDHEIM, J. EFSKIND, *Tetrahedron* **2000**, *56*, 4847–4857.
- 41 For diyne metathesis reactions using ruthenium allenylidene complexes, see: A. FÜRSTNER, A. F. HILL, M. LIEBL, J. D. E. T. WILTON-ELY, *Chem. Commun.* **1999**, 601–602.
- 42 T. KITAMURA, M. MORI, *Org. Lett.* **2001**, *3*, 1161–1163.
- 43 (a) A. RÜCKERT, D. EISELE, S. BLECHERT, *Tetrahedron Lett.* **2001**, *42*, 5245–5247. (b) S. RANDL, N. LUCAS, S. J. CONNON, S. BLECHERT, *Adv. Synth. Catal.* **2002**, *344*, 631–633.
- 44 M. ULMAN, R. H. GRUBBS, *Organometallics* **1998**, *17*, 2484–2489.
- 45 (a) D. BANTI, M. NORTH, *Tetrahedron Lett.* **2002**, *43*, 1561–1564. (b) D. BANTI, M. NORTH, *Adv. Synth. Catal.* **2002**, *344*, 694–704.
- 46 (a) B. M. TROST, G. J. TANOURY, *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638.
(b) B. M. TROST, M. K. TROST, *J. Am. Chem. Soc.* **1991**, *113*, 1850–1852.
(c) B. M. TROST, M. J. TROST, *Tetrahedron Lett.* **1991**, *32*, 3647–3650.
(d) B. M. TROST, M. YANAI, K. HOOGSTEEN, *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295.
- 47 N. CHATANI, T. MORIMOTO, T. MUTO, S. MURAI, *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050.
- 48 (a) N. CHATANI, N. FURUKAWA, H. SAKURAI, S. MURAI, *Organometallics* **1996**, *15*, 901–903. (b) N. CHATANI, K. KATAOKA, S. MURAI, *J. Am. Chem. Soc.* **1998**, *120*, 9104–9105. (c) A. FÜRSTNER, H. SZILLAT, F. STELZER, *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786. (d) A. FÜRSTNER, F. STELZER, H. SZILLAT, *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.
- 49 N. CHATANI, H. INOUE, T. KOTSUMA, S. MURAI, *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295.
- 50 For the application of enyne rearrangements of this type in natural product synthesis, see: (a) A. FÜRSTNER, H. SZILLAT, B. GABOR, R. MYNOTT, *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314.
(b) B. M. TROST, G. A. DOHERTY, *J. Am. Chem. Soc.* **2000**, *122*, 3801–3810.
- 51 J.-U. PETERS, S. BLECHERT, *Chem. Commun.* **1997**, 1983–1984.
- 52 G. B. HOVEN, J. EFSKIND, C. RÖMMING, K. UNDHEIM, *J. Org. Chem.* **2002**, *67*, 2459–2463.
- 53 B. WITULSKI, T. STENGEL, J. M. FERNÁNDEZ-HERNÁNDEZ, *Chem. Commun.* **2000**, 1965–1966.
- 54 S. K. DAS, R. ROY, *Tetrahedron Lett.* **1999**, *40*, 4015–4018.
- 55 K. P. C. VOLLHARDT, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539–555.
- 56 S. J. NEESON, P. J. STEVENSON, *Tetrahedron Lett.* **1988**, *29*, 813–814.
- 57 For recent reviews on cyclotrimerisations of alkynes, see: (a) S. SAITO, Y. YAMAMOTO, *Chem. Rev.* **2000**, *100*, 2901–2915. (b) D. B. GROTHJAHN, Transition Metal Alkyne Complexes: Transition Metal-Catalyzed Cyclotrimerization in *Comprehensive Organometallic Chemistry II*, Vol. 12, E. W. ABEL, F. G. A. STONE, G. WILKINSON (Eds.), L. S. HEGEDUS (Vol. Ed.), Pergamon, Oxford, 1995, pp. 741–770. (c) M. LAUTENS, W. KLUTE, W. TAM, *Chem. Rev.* **1996**, *96*, 49–92.
- 58 R. STRAGIES, M. SCHUSTER, S. BLECHERT, *Chem. Commun.* **1999**, 237–238.
- 59 J. A. SMULIK, S. T. DIVER, *Tetrahedron Lett.* **2001**, *42*, 171–174.

2.5

Ene-Yne Metathesis

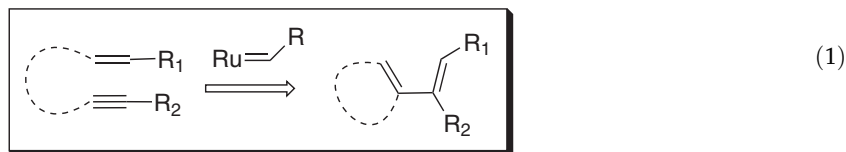
Miwako Mori

2.5.1

Introduction

Enyne metathesis is a unique and interesting reaction. In this reaction, double and triple bonds are cleaved and a double bond is simultaneously formed. As a result, the alkylidene parts of the double bond are introduced onto the respective alkyne carbons to give a diene moiety, and the initial triple bond is converted into a single bond (Eq. (1)) [1].

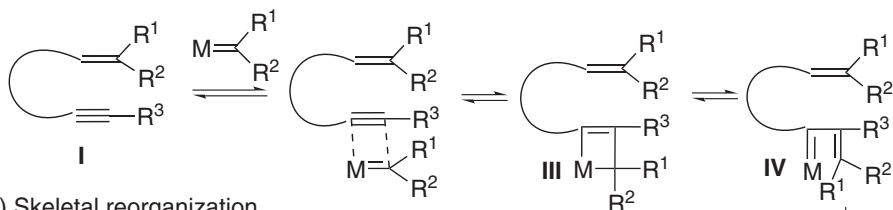
Enyne metathesis



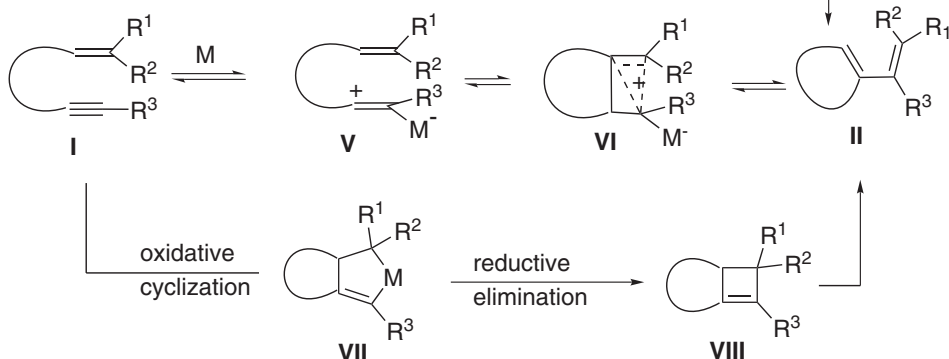
Enyne metathesis is therefore called skeletal reorganization. This reaction is catalyzed by a transition metal. However, due to the difficulty of controlling this reaction, in the past it had been used only as an intramolecular reaction. However, an intermolecular cross-metathesis reaction of alkene and alkyne has since been developed.

Two types of enyne metathesis are known. One is a transition metal-carbene complex-mediated or -catalyzed reaction. As transition metals, tungsten, molybdenum, chromium, and ruthenium carbene complexes are known to mediate or catalyze the reaction. This reaction formally proceeds by a [2+2] cycloaddition between the multiple bond of **I** and the carbene complex to give metallacyclobutene **III**. Ring opening of **III** gives carbene complex **IV**, which reacts with olefin intramolecularly to give cyclized diene **II**. The other is a so-called skeletal reorganization, which is catalyzed by transition metals such as palladium, platinum, iridium, and ruthenium complexes. Recently, a gallium-catalyzed skeletal reorganization

i) Transition metal-carbene complex-catalyzed reaction



ii) Skeletal reorganization

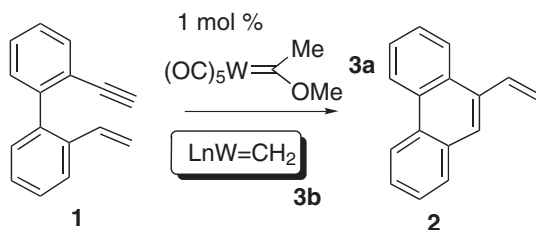


Scheme 2.5-1. Enyne metathesis.

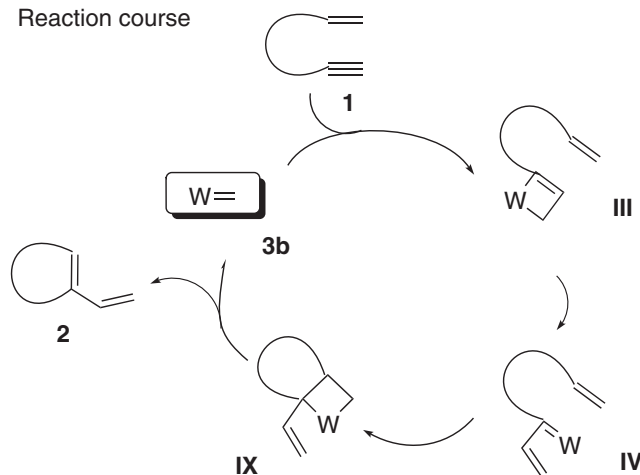
has been reported [2c]. The mechanism underlying skeletal reorganization is not clear. Presumably, the transition metal coordinates to the triple bond to give **V** and then the alkene carbon reacts with the alkyne part to form **VI**. Then it would be converted into **II**. Trost developed an enyne metathesis reaction using palladium catalyst [3]. This reaction would be one of skeletal reorganization. This reaction proceeds via oxidative cyclization of enyne and reductive elimination to form cyclobutene **VIII**, whose ring opening gives **II**.

Enyne metathesis was first discovered by Katz [4] in 1985 using a Fischer tungsten-carbene complex (**3a**). The reaction of enyne **1** with Fischer tungsten-carbene complex **3a** affords compound **2** in 31% yield. Thus, this reaction is called a methylene migration reaction, and the real species for this reaction is a methylene tungsten-carbene complex (**3b**). The reaction proceeds via formal [2+2] cycloaddition of carbene complex **3b** and the alkyne part as shown in Scheme 2.5-2.

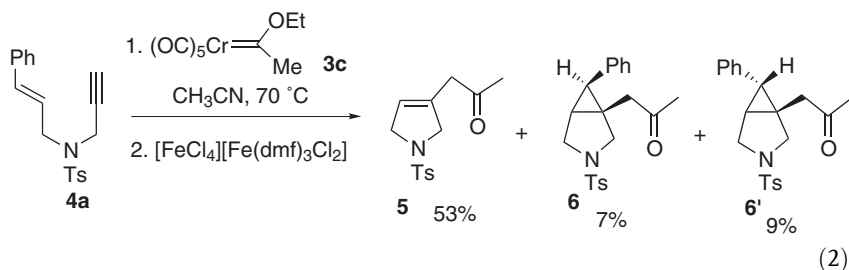
Then Mori reported chromium-mediated and -catalyzed enyne metathesis [5]. When enyne **4a** was treated with Fischer chromium-carbene complex **3c** followed by hydrolysis, metathesis product **5** was obtained in 53% yield along with carbene insertion products **6** and **6'** (Eq. (2)). This reaction was further developed as a chromium-catalyzed enyne metathesis when the enyne has the same substituent on the alkene moiety as that of Fischer chromium-carbene complex **3c**. Treatment of *E*- and *Z*-**4b** with 10 mol% of chromium-carbene complex **3c** followed by hydrolysis afforded the same compound (**5**) (Scheme 2.5-3).



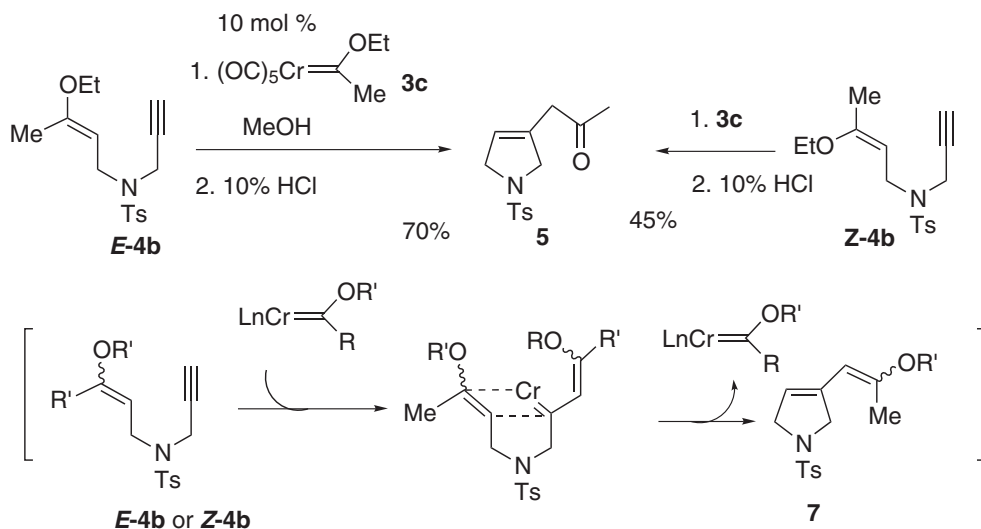
Reaction course



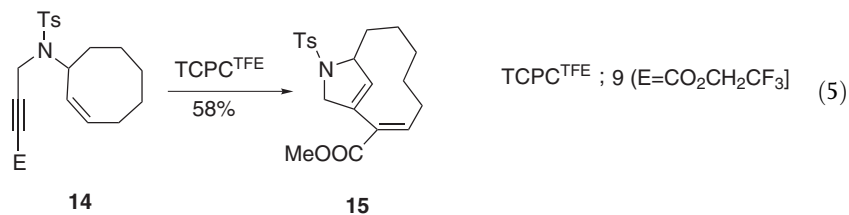
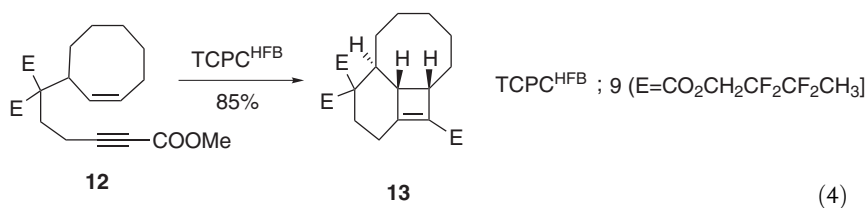
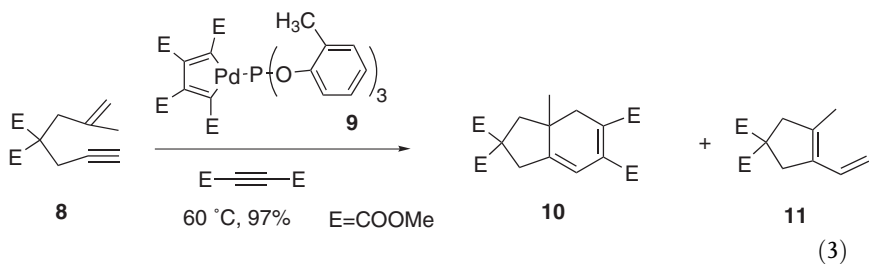
Scheme 2.5-2. Tungsten-catalyzed enyne metathesis.



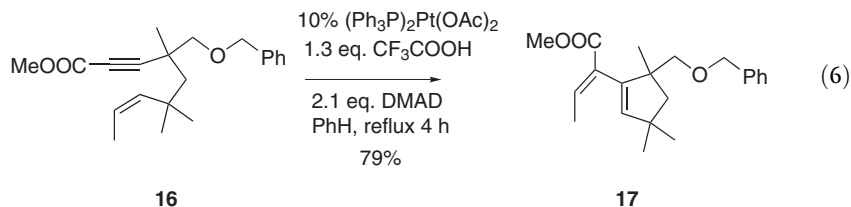
Trost reported a palladium-catalyzed enyne metathesis during his study on palladium-catalyzed enyne cyclization [3]. Treatment of 1,6-enyne **8** with palladacyclopentadiene (TCPT, **9**) in the presence of tri-*o*-tolylphosphite and dimethylacetylene dicarboxylate (DMAD) led to the formation of cycloadduct **10** and vinylcyclopentene **11** (Eq. (3)). The latter compound **11** is clearly a metathesis product. To confirm the formation of cyclobutene as an intermediary in this reaction, Trost obtained **13** by treatment of **12** with TCPC in high yield (Eq. (4)). This method provides a very simple route to bridged bicycles such as **15** possessing bridgehead olefin (Eq. (5)).



Scheme 2.5-3. Chromium-catalyzed enyne metathesis.



Trost also reported metathesis of enoate using a simple platinum complex (Eq. (6)) [3b].



Furthermore, Murai and Chatani reported the skeletal reorganization reactions using various transition metals [2a].

2.5.2

Transition Metal-Carbene Complex-Catalyzed Enyne Metathesis

2.5.2.1

Ring-Closing Metathesis (RCM) of Enyne Using Ruthenium Carbene Complex

Grubbs [6] and Schrock [7] recently discovered very reactive carbene complexes for olefin metathesis. Many cyclic compounds were synthesized from dienes using these carbene complexes (**18**) [6b].

Grubbs also developed an elegant method for dienyne metathesis using a ruthenium-carbene complex (**18**) [6c,d]. When a benzene solution of **20** was stirred at room temperature in the presence of 3 mol% of ruthenium-carbene complex **18a**, bicyclic compound **21** was obtained in 95% yield via tandem cyclization.

Mori developed a method for enyne metathesis using ruthenium-carbene complex **18a** or **18b** [8]. A benzene or CH_2Cl_2 solution of enyne **22** was stirred in the presence of a catalytic amount of **18a** or **18b** at room temperature to give cyclic compound **23** in high yield. Using this method, 5- to 9-membered carbo- and

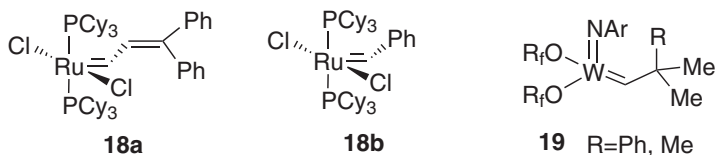
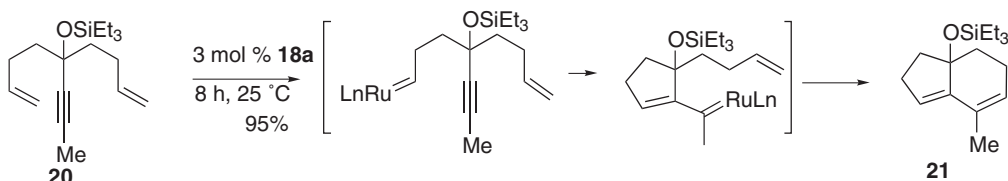
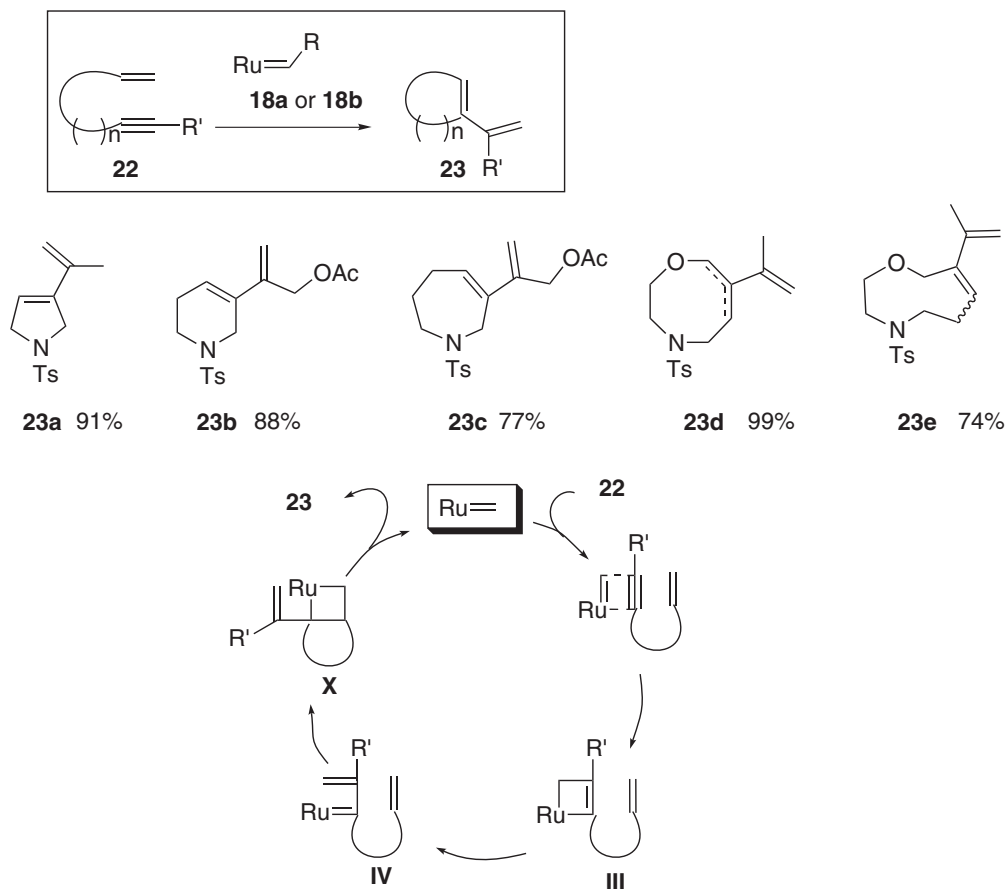


Fig. 2.5-1.



Scheme 2.5-4. Ruthenium-catalyzed dienyne metathesis.

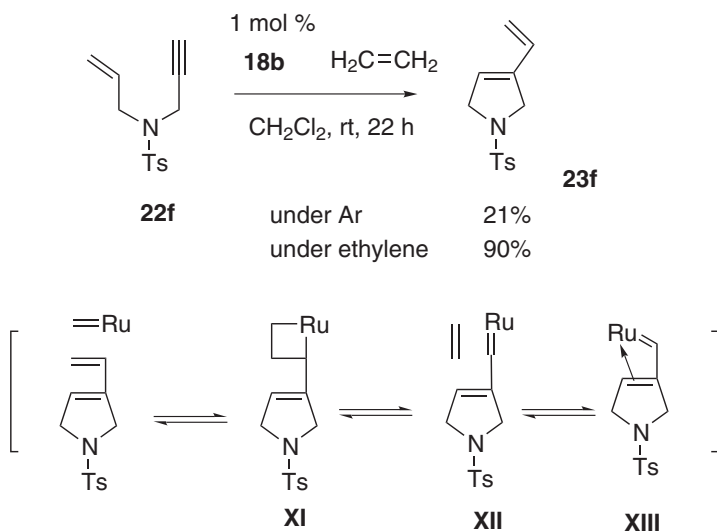


Scheme 2.5-5. Ruthenium-catalyzed enyne metathesis.

heterocyclic compounds **23** were synthesized from the corresponding enynes in high yields.

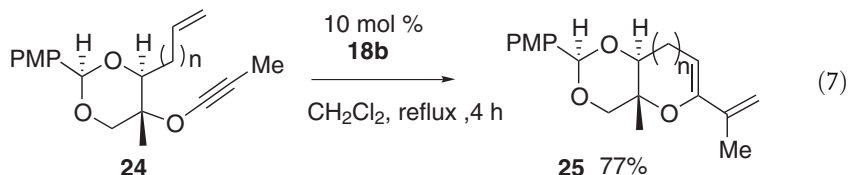
The reaction proceeds by [2+2] cycloaddition of carbene complex and the alkyne part of **22** to form **III**, and ring opening of this complex gives **IV**, which reacts with the alkene part intramolecularly to afford **X**. Ring opening of this complex gives **23**, and a methyldene carbene complex was reproduced. Even if the reaction starts from [2+2] cycloaddition of carbene complex and the alkene part, a similar reaction pathway should be followed.

In this reaction, although enynes having disubstituted alkyne afforded cyclized compounds in high yields, enynes having terminal alkyne did not give good results. Presumably, the terminal alkene part of the product **23f** reacts with carbene complex to afford ruthenium carbene complex **XIII** coordinated by alkene. Such a reaction was carried out under ethylene gas to give desired compound **23f** in high yield, because methyldene-carbene complex would be regenerated from complex **XIII** under ethylene gas [8b].

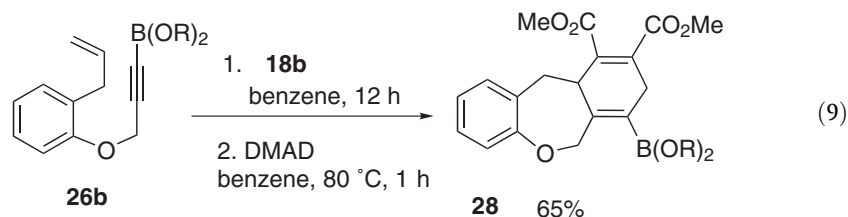
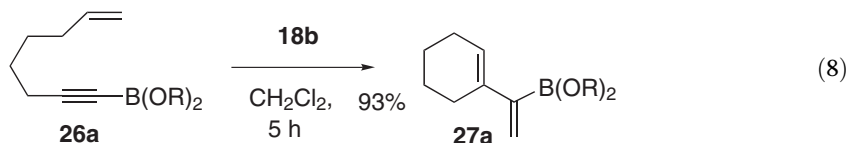


Scheme 2.5-6. Terminal alkyne-ene metathesis.

RCM of enyne was used for the synthesis of various useful compounds. Clark reported the synthesis of alkenyl-substituted cyclic enol ether **25** from alkynyl ether **24** using **18b** (Eq. (7)) [9].



Conversion of en-1-ynylboronic esters **26** into 5- to 7-membered carbocyclic and heterocyclic 1,3-dialkenyl-2-boronates **27** was achieved by enyne metathesis. Enyne **26a** was reacted with **18b** to give cyclized compound **27a** in high yield (Eq. (8)). The diene moiety of the product formed in this reaction was reacted with DMAD to afford tricyclic compound **28** (Eq. (9)) [10].



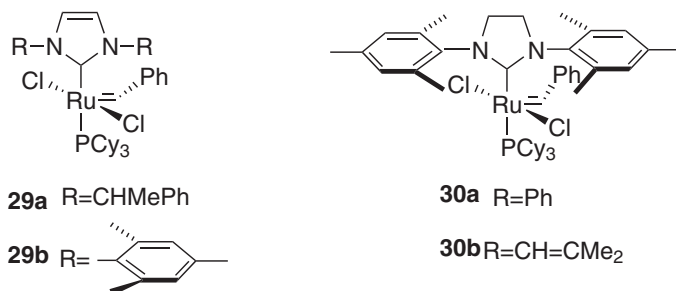


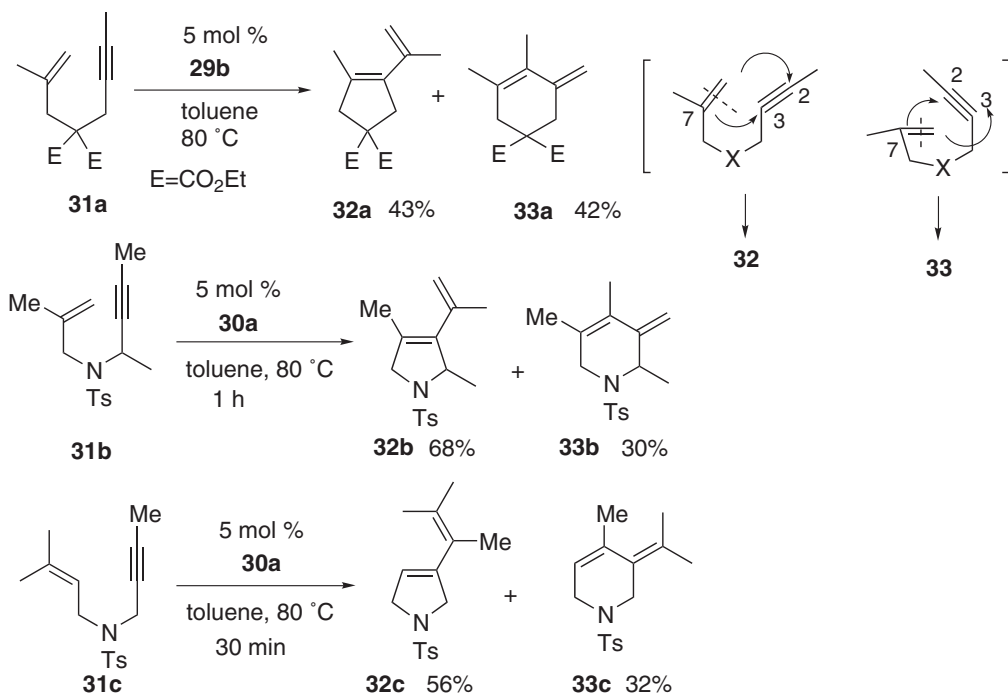
Fig. 2.5-2. Second-generation ruthenium-carbene complexes.

Recently, Herrmann, Nolan, and Grubbs have developed various ruthenium-carbene complexes having heterocyclic carbene as a ligand [11]. These complexes are called second-generation ruthenium-carbene complexes, and it is known that the reactivities of these complexes are greater than those of the first-generation ruthenium-carbene complexes (18). It is quite interesting that cross olefin metathesis was realized by using these catalysts [12].

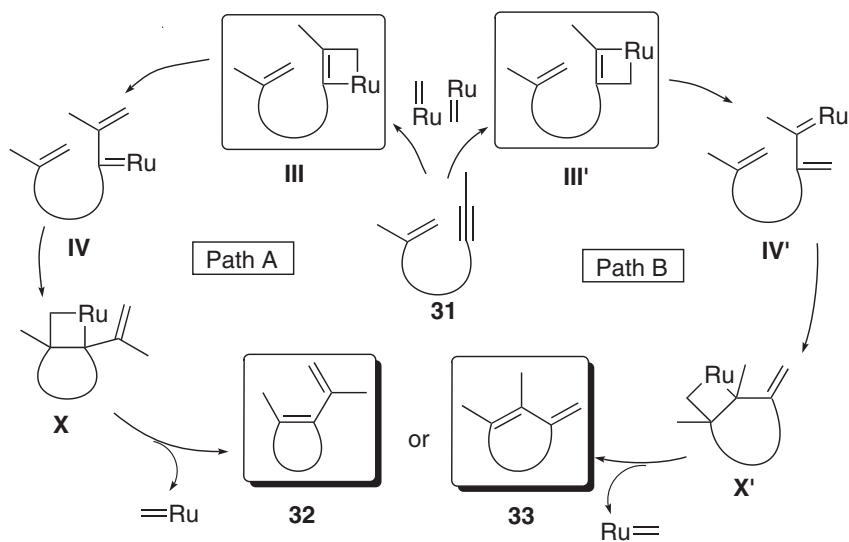
Grubbs studied the detailed reaction mechanism using complex 30, and he reported that the olefin metathesis reaction should be carried out upon heating in toluene or CH₂Cl₂ in order to effect dissociation of the phosphine ligand from 30 [12b].

Mori reinvestigated ring-closing enyne metathesis using ruthenium-carbene complexes 29b or 30b [13]. When a toluene solution of enyne 31a having 1,1-disubstituted alkene was warmed at 80 °C for 5 h in the presence of 5 mol% 29b, two metathesis products, 32a and 33a, were obtained in 85% yields. The former compound 32a has a 5-membered ring, which was usually formed by the reaction of an enyne having mono- or 1,2-disubstituted alkene using 18b. This would be produced by carbon-carbon bond formation between the disubstituted alkene carbon (C7) and the inside carbon (C3) of alkyne, and the methylene carbon of disubstituted alkene would migrate to the outside carbon (C2) of alkyne. The latter compound 33a should be produced by carbon-carbon bond formation between the disubstituted alkene carbon (C7) and the outside alkyne carbon (C2), and the methylene carbon of alkene would migrate to the inside alkyne carbon (C3). Various enynes having di- or trisubstituted alkene were examined, and similar results were obtained.

A possible reaction course is shown in Scheme 2.5-8. Two pathways should be considered in the reaction of the alkyne part of enyne 31 with methyldiene ruthenium-carbene complex. If the reaction proceeds through path A, [2+2] cycloaddition occurs between the alkyne part and the ruthenium-carbene complex. In this case, ruthenium metal connects with the inside carbon of alkyne to produce metallacyclobutene III, which is converted into IV. Intramolecular [2+2] cycloaddition affords X. Thus, a smaller ring-size product (5-membered ring) is formed. However, when ruthenium metal of carbene complex connects with the outside carbon of the alkyne (path B), ruthenacycle III' would be formed, and it would be converted into ruthenium carbene complex IV' by ring opening. Then it would



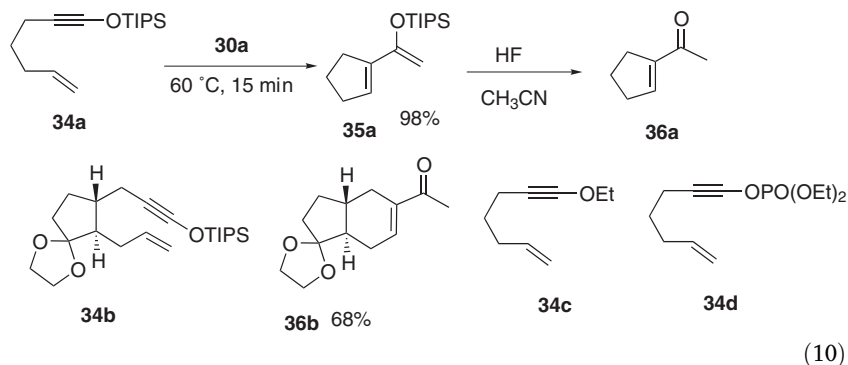
Scheme 2.5-7. Enyne metathesis using second-generation ruthenium-carbene complex.



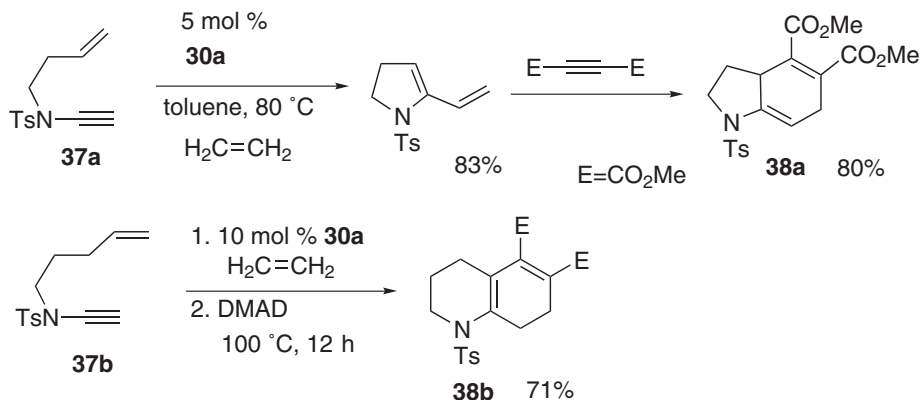
Scheme 2.5-8. Possible reaction course for formation of two metathesis products.

react with the alkene part intramolecularly to give ruthenacyclobutane **X'**, which would afford a 6-membered ring compound. Various enynes were examined and it was found that enynes having disubstituted alkyne and di- or trisubstituted alkene afforded two metathesis products, but the reason for this is not clear.

Kozmin reported siloxyalkyne-alkene metathesis using second-generation ruthenium-carbene complex **30a** [14]. The reaction of **34a** proceeded smoothly in the presence of **30a**, and the desired product **35a** was obtained in high yield. Deprotection of the silyl group of the metathesis product **35a** afforded methyl ketone **36a**. In a similar manner, compound **36b** was obtained from **34b** in 68% yield. Interestingly, in the case of ethoxyalkyne **34c** or alkynyl phosphate **34d**, no detectable amount of the corresponding metathesis product was formed.



Metathesis reaction of ene-ynamide **37a** using **30a** under ethylene gas afforded a pyrrolidine derivative having a dienamide moiety [15]. The use of first-generation ruthenium-carbene complex **18b** afforded a small amount of this compound. Diels-Alder reaction of the cyclized products with DMAD proceeded smoothly to afford indole **38a** and quinoline **38b** derivatives in high yields.



Scheme 2.5-9. Ring-closing metathesis of ene-ynamide.

2.5.2.2

Ring-Opening Metathesis–Ring-Closing Metathesis of Cycloalkene-Yneo

Ring-opening metathesis–ring-closing metathesis (ROM-RCM) of an enyne containing a cycloalkene moiety is very interesting because the double bond of cycloalkene cleaves and an alternative ring system is formed during the reaction. When a CH_2Cl_2 solution of **39a** was stirred in the presence of 10 mol% **18b** under ethylene gas, the reaction proceeded smoothly to give pyrrolidine derivative **40a** in good yield. Various cycloalkene-yne **39** afforded pyrrolidine derivatives **40** with different carbon chains corresponding to the ring size of the starting cycloalkene **39**. Under argon gas, no metathesis product was formed, although the starting material was completely consumed. The formally designated reaction is shown in Figure 2.5-3. The multiple bonds of the cycloalkene and alkyne of **39** and ethylene are cleaved; each methylene part of ethylene is introduced on the alkene and alkyne carbons, respectively; and a double bond is formed between the cycloalkene carbon and the alkyne carbon to give pyrrolidine derivative **40** [16a].

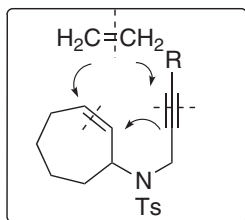
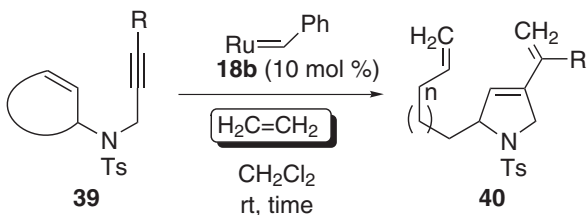


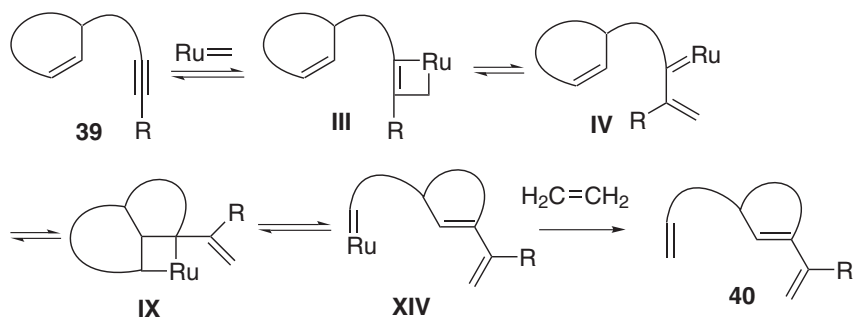
Fig. 2.5-3.

Scheme 2.5-10. ROM-RCM of enyne **39**.

Tab. 2.5-1. ROM-RCM of enyne containing cycloalkene moiety.

Run		R	Ring size	n	Time (h)		Yield (%) ^a
1	39a	Me	7	2	24	40a	56 ^b
2	39b	H	6	1	4	40b	78
3	39c	H	7	2	1	40c	70
4	39d	H	8	3	1	40d	75

^a) Yields were calculated from ^1H NMR. ^b) **39a** was recovered in 36% yield.



Scheme 2.5-11. Reaction course of ROM-RCM of enyne containing cycloalkene moiety.

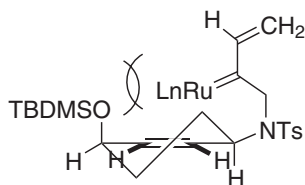


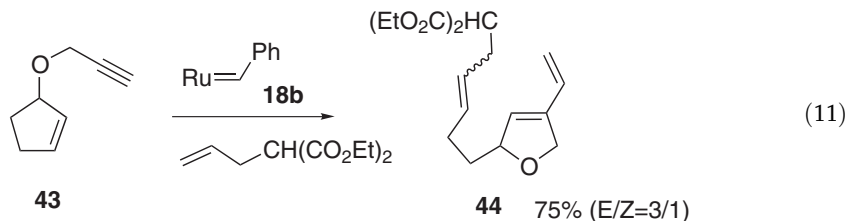
Fig. 2.5-4.

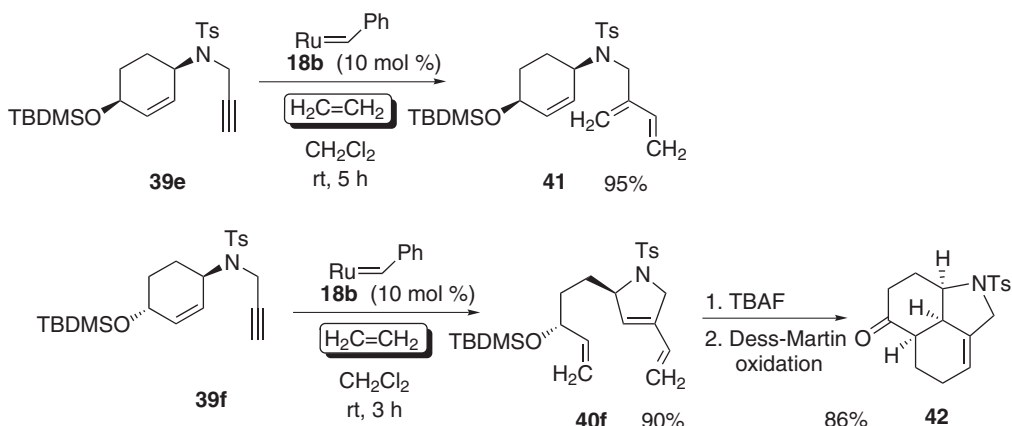
A possible reaction course is shown in Scheme 2.5-11. [2+2] Cycloaddition of an alkyne carbon and metal-carbene complex affords metallacyclobutene **III**.

Ring opening of **III** gives ruthenium-carbene complex **IV**, which reacts with the cycloalkene part to give ruthenacyclobutane **IX**, whose ring opening occurs to give ruthenium-carbene complex **XIV**. This reacts with ethylene to give **40**.

When enyne **39e** having *cis*-substituents on the cyclohexene ring was treated in a similar manner, triene **41** was formed. Presumably, due to steric hindrance between the silyloxy group and the ruthenium metal (Figure 2.5-4), the ruthenium-carbene complex cannot react with the double bond of the cyclohexene ring, but it reacts with ethylene to give **41**. On the other hand, enyne **39f** having *trans*-substituents on the cyclohexene ring afforded pyrrolidine derivative **40f** in high yield. Deprotection of the silyl group followed by Dess-Martin oxidation gave tricyclic compound **42** in high yield.

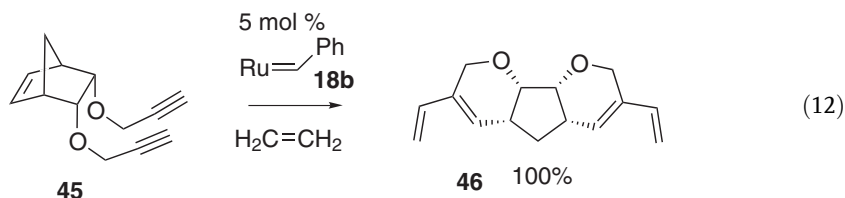
Bleichert reported ROM-RCM of enyne **43** in the presence of ethyl allylmalonate using **18b**. In this reaction, furan derivative **44** was obtained in 75% yield (Eq. (11)) [17].





Scheme 2.5-12. ROM-RCM of enyne.

Norbornene derivative **45** bearing propargyloxy substituents in the 5 and 6 positions undergoes a cascade series of enyne metatheses when treated with **18b**, leading to the formation of heterocyclic diene **46** [18].

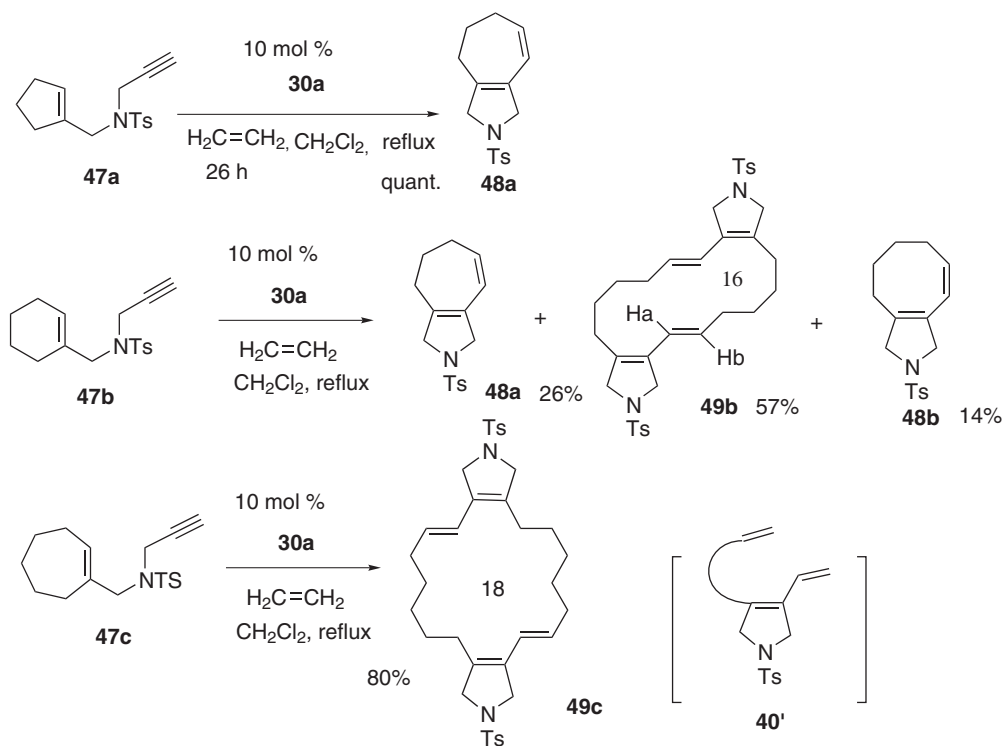


The ROM-RCM of cycloalkene-yne **47** afforded unexpected products [16b]. Although enyne **47a** having a cyclopentene moiety was treated with the second-generation ruthenium-carbene complex **30a** in CH_2Cl_2 to give the desired bicyclic compound **48a** in quantitative yield, enyne **47b** afforded the unexpected products **48a** and **49b**, and expected product **48b** was obtained in only 14% yield. Moreover, enyne **47c** afforded only dimeric compound **49c** in 80% yield. Presumably, isomerization of the double bond of **40'** would occur due to the action of ruthenium carbene complex **30a** and the thermodynamic product would be formed under the reaction conditions.

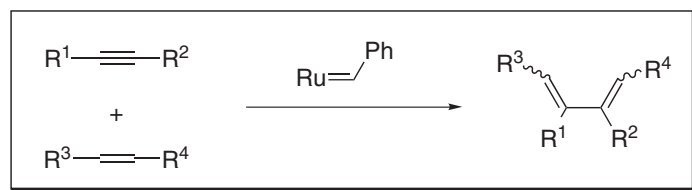
2.5.2.3

Intermolecular Enyne Metathesis (Cross-Metathesis)

Intermolecular enyne metathesis (cross-metathesis, CM) is a unique and interesting reaction if it can be achieved, but it is very difficult because it involves olefin metathesis, enyne metathesis, and diyne metathesis. It is likely that various olefins, dienes, and polymers would be formed by intermolecular enyne metathesis.



Scheme 2.5-13. ROM-RCM of cycloalkene-yne.



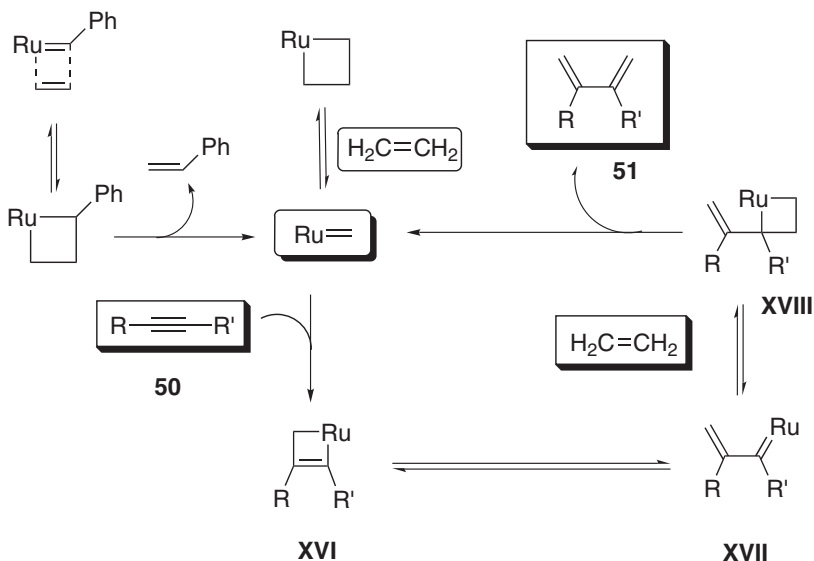
Scheme 2.5-14. Intermolecular enyne metathesis.

To solve this problem, ethylene gas was used as an alkene, and a method for 1,3-diene synthesis from alkyne was developed using cross enyne metathesis [19a]. The reaction course is shown in Scheme 2.5-15. Methylidene-carbene complex reacts with alkyne **50** to give ruthenacyclobutene **XVI**.

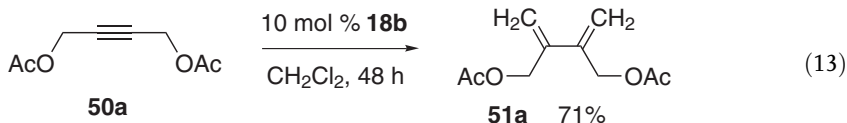
Ring opening of **XVI** affords ruthenium-carbene complex **XVII**, which reacts with ethylene and not alkyne, because ethylene is a very reactive species and this reaction is carried out under ethylene gas. Ring opening of complex **XVIII** affords 1,3-diene **51**. The reaction procedure is very simple. That is, a CH_2Cl_2 solution of alkyne **50a** is stirred in the presence of ruthenium-carbene complex **18b** at room temperature under an atmosphere of ethylene gas for 48 h to give 1,3-diene **51a** in 71% yield (Eq. (13)).



Pathway of intermolecular enyne metathesis



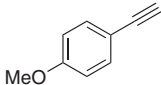
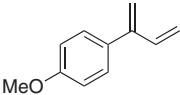
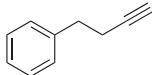
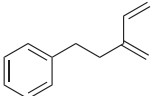
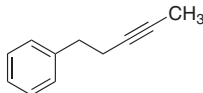
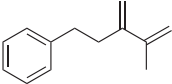
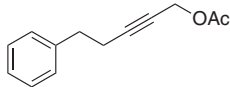
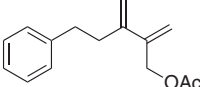
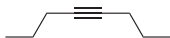
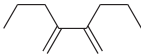
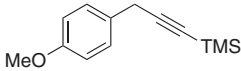
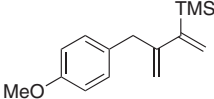
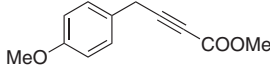
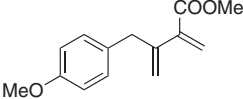
Scheme 2.5-15. Plan for 1,3-diene synthesis using intermolecular enyne metathesis.



In this reaction, an alkyne having a heteroatom at the propargylic position is required to obtain a good result when the first-generation ruthenium-carbene complex **18b** is used. However, the second-generation ruthenium-carbene complex **30a** is very effective, and various alkynes, such as terminal or internal alkynes and the alkynes having a silyl or a carbomethoxy group, can be converted into 1,3-diene **51** [19b,c].

Blechert reported cross enyne metathesis between the terminal alkyne and alkene. The reaction is carried out in CH_2Cl_2 at room temperature with 5–7 mol% of **18b** [20]. Reported yields of **52** were achieved within 12–48 h using a two- to threefold excess of alkene. The products were obtained as a mixture of *E*- and *Z*-isomers in a ratio of 1:1 to 1:3. Because of this lack of stereochemical course,

Tab. 2.5-2. Synthesis of various 1,3-dienes.

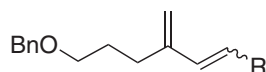
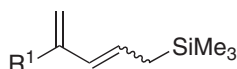
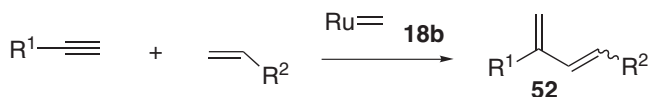
Run	Alkyne 50	Diene 51	Temp. (°C)	Time (h)	Yield (%)
1			80 ^{a)}	0.5	88
2			80 ^{a)}	0.5	71
3			80 ^{a)}	0.5	85
4			80 ^{a)}	0.5	100
5			reflux ^{b)}	24	80
6			80 ^{a)}	16	87 ^{c)}
7			80 ^{a)}	16	43 ^{d)}

All reactions were carried out using 5 mol% of **30a** under 1 atm. pressure of ethylene gas. ^{a)} In toluene. ^{b)} In CH₂Cl₂. ^{c)} Starting material, 10%. ^{d)} Starting material, 34%.

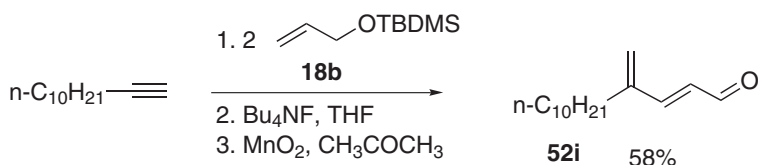
Blechert used TBDMS-protected allyl alcohol and deprotection of the metathesis product followed by oxidation to give the desired *E*-isomer **52i** in an overall yield of 58%.

Blechert later reported polymer-supported synthesis of 1,3-diene by an efficient ruthenium-catalyzed selective ene-yne cross metathesis followed by cleavage from the polymer using Pd(0). The group used polystyrene resin **53** containing a propargyl ester moiety, and the metathesis product linked with polymer was cleaved by the Pd(0) catalyst. As a result, **55a** and **55b** were obtained in good yields as a mixture of *E*- and *Z*-isomers [20b].

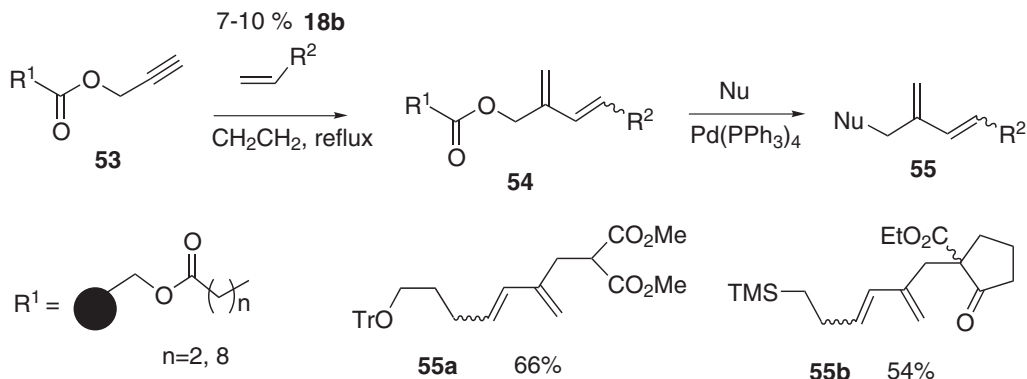
Furthermore, a short and efficient method for synthesis of tetrahydropyridines could be achieved by a combination of enyne cross-metathesis and aza-Diels-Alder



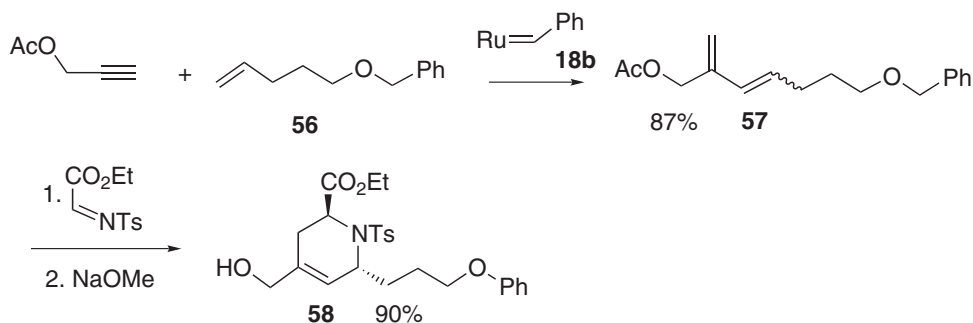
	R ¹	Yield (%)		R	Yield (%)
52a	CH ₂ OTHP	81	52e	CH ₂ SiMe	86
52b	CH ₂ OAc	90	52f	CH ₂ ^t Bu	82
52c	CH(CH ₃)OAc	63	52g	(CH ₂) ₂ CH(CO ₂ Me) ₂	76
52d	CH ₂ OCO ₂ Me	89	52h	CH ₂ OTBDMS	83



Scheme 2.5-16. Cross-coupling of terminal alkyne and alkene.

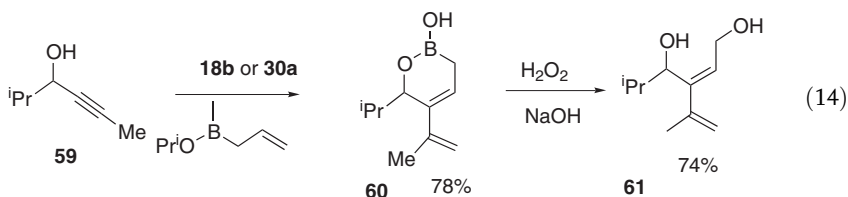
Scheme 2.5-17. [Ru]-catalyzed binding of olefins to resin **53** and Pd(0)-catalyzed nucleophilic cleavage of the resulting 1,3-dienes **54**.

reaction under high pressure [20c]. Compound **57** was obtained in high yield from olefin **56** and propargyl acetate as a mixture of *E*- and *Z*-isomers (0.8 to 1.5). Aza-Diels-Alder reaction of **57** provided a piperidine derivative, which was then equilibrated with NaOMe in MeOH to give **58** as a single diastereomer in high yield.

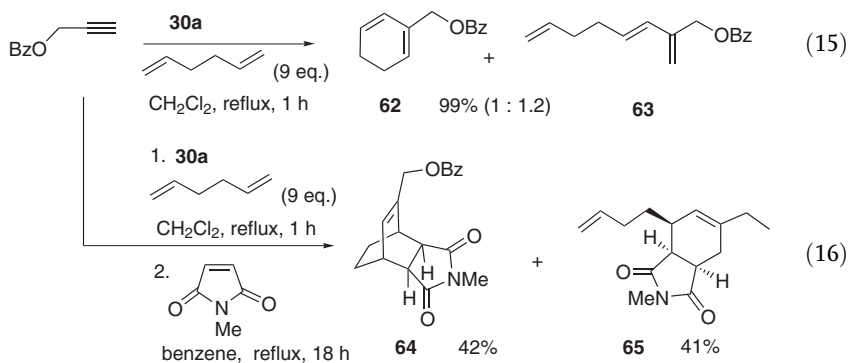


Scheme 2.5-18. Synthesis of substituted tetrahydropyridines.

Transesterification of unsaturated boric ester with allyl or propargylic alcohol provided mixed organoboronic ester, which could be trapped using ring-closing metathesis to afford cyclic boronic ester **60** [21]. Oxidation of **60** gave diol **61** (Eq. (14)).



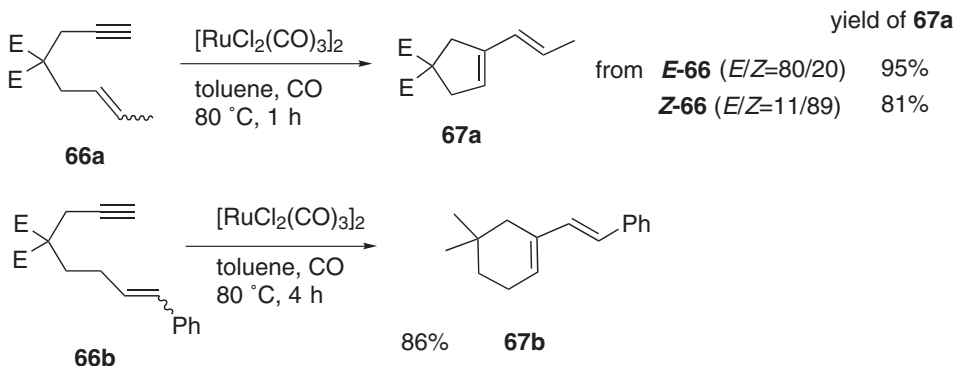
Diver reported tandem dienyne cross-metathesis/ring-closing metathesis between terminal alkynes and 1,5-hexadiene. In addition, a mixture of metathesis products **62** and **63** was subjected to Diels-Alder reaction with *N*-methylmaleimide, yielding the corresponding cycloadducts **64** and **65** in one synthetic step [22].



2.5.3

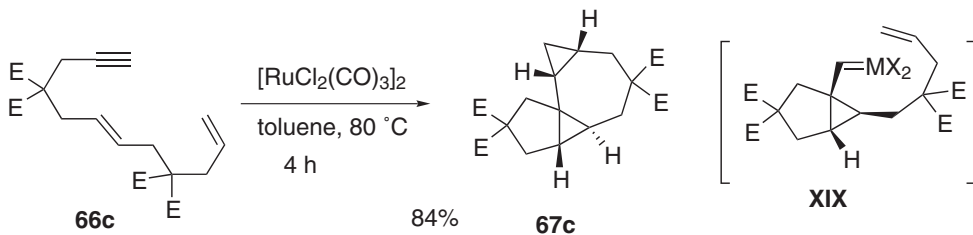
Skeletal Reorganization Using Transition Metals

After Trost's first report of skeletal reorganization using palladium and platinum complexes, Murai and Chatani reported ruthenium-catalyzed skeletal reorganization of 1,6-enyne [2a]. They used $[\text{RuCl}_2(\text{CO})_3]_2$ as a catalyst, and the reaction was carried out under carbon monoxide. Reaction of *E*-**66a** or *Z*-**66a** afforded only *E*-isomer **67a**. The reaction of an *E/Z* mixture of 1,7-enyne **66b** afforded only *E*-isomer of 1-vinylcyclohexene **67b** in 86% yield.



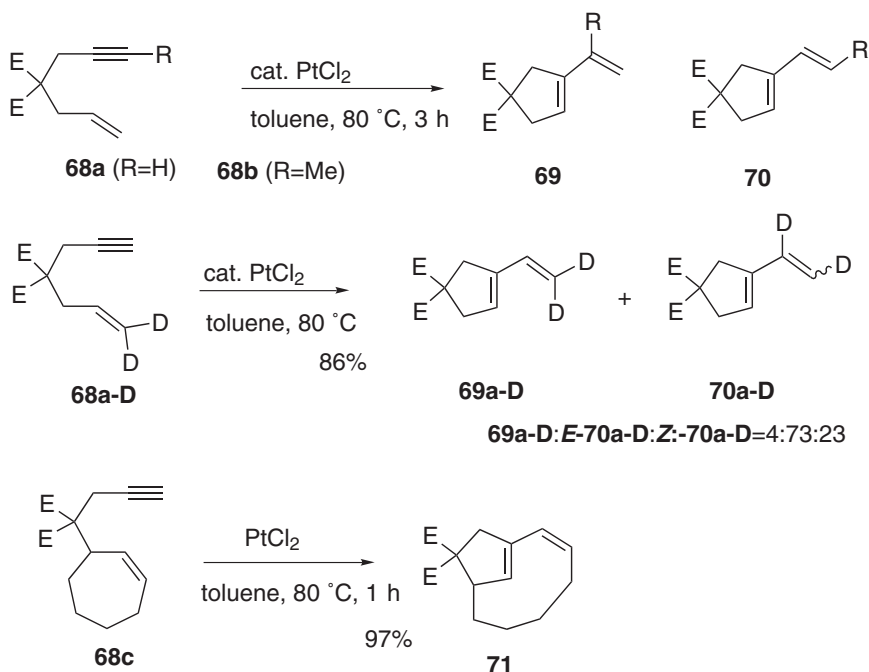
Scheme 2.5-19. Ruthenium-catalyzed skeletal reorganization.

Murai and Chatani considered carbenoid as an intermediate and attempted to trap this [2b]. The reaction of 6,11-dien-1-yne **66c** in toluene in the presence of $[\text{RuCl}_2(\text{CO})_3]_2$ at 80 °C for 4 h gave tetracyclic compound **67c** in 84% yield. The reaction involves two cyclopropanation reactions. This indicates that two carbenoid carbons **XIX** would be generated on the alkyne carbons during the reaction.



Scheme 2.5-20. Trap of carbenoid intermediate.

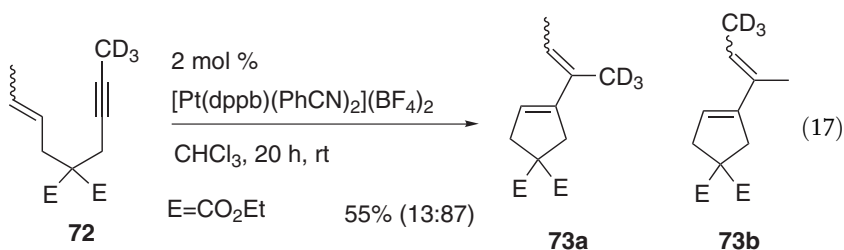
Murai and Chatani also reported platinum-catalyzed skeletal reorganization of 1,6- and 1,7-enyne **68** to 1-vinylalkene **69** [23]. The reaction of **68b** with PtCl_2 gave **69b** and **70b** (ratio of 8:1). The formation of **70b** is very interesting with respect to the reaction mechanism, because it involves an unusual change in the bond relationship. An anomalous C–C bond formation also occurred in the reaction of **68a-D**. Formation of **70a-D** indicates the occurrence of unusual bond fission. The



Scheme 2.5-21. Platinum-catalyzed skeletal reorganization.

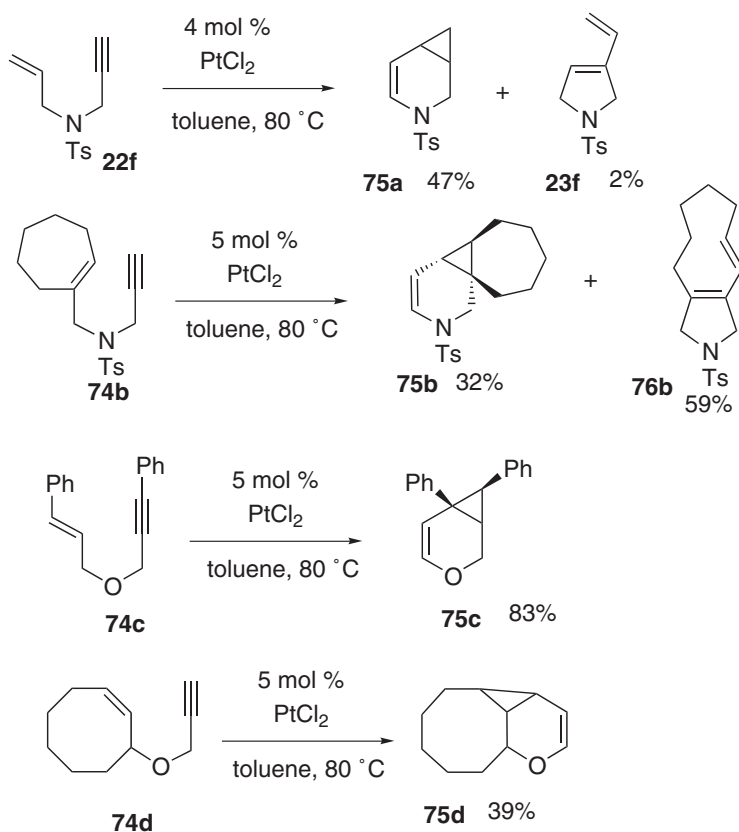
platinum-catalyzed reaction of **68c** gave exclusively bicyclic compound **71** in 97% yield.

The skeletal reorganization of 1,6-enynes into 1-vinylcyclopentenones was catalyzed by a cationic platinum complex under mild conditions (Eq. (17)) [24].



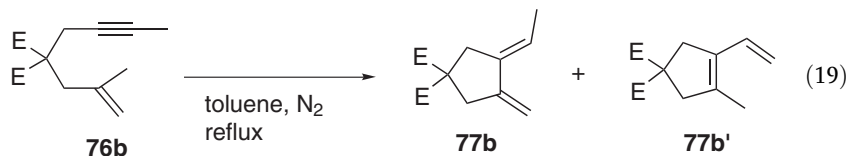
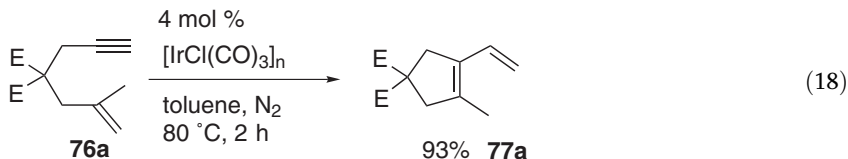
Fürstner reported that the skeletal reorganization of enyne **22f** containing a nitrogen atom in a tether between the alkene and alkyne moiety led to the formation of bicyclo[4.1.0]heptene **75a** and a small amount of corresponding 1,3-diene product **23f** originating from the formal metathesis [25]. Enyne containing an oxygen atom in the tether gave a similar result, and only **75c** or **75d** was formed from **74c** or **74d**.

Skeletal reorganization using iridium complex was reported by Chatani and Murai (Eqs. 18 and 19) [26]. Treatment of enyne having a methyl group on the

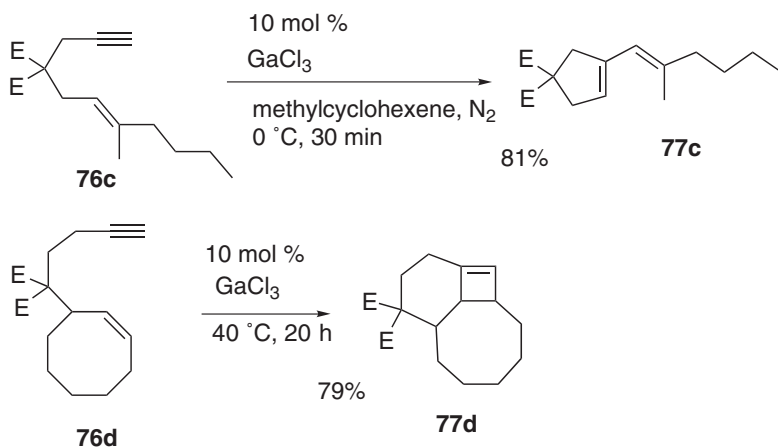


Scheme 2.5-22. Formation of cyclopropane derivatives catalyzed by PtCl_2 .

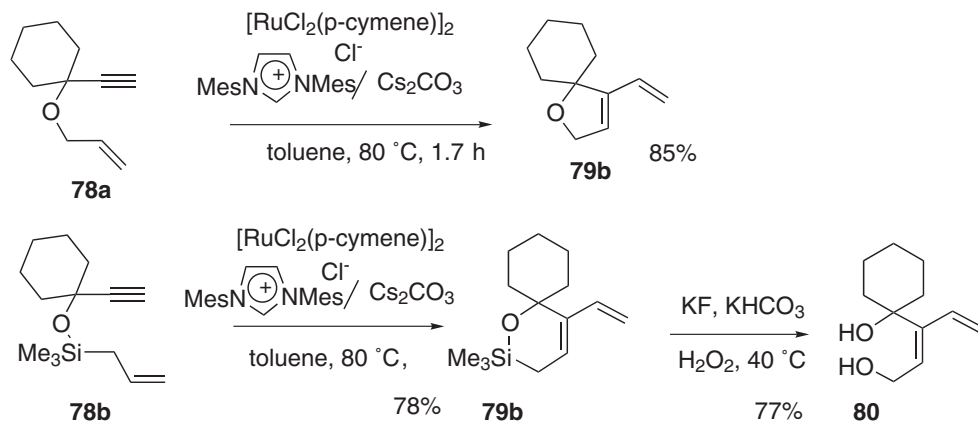
alkyne with $[\text{IrCl}(\text{CO})_3]_n$ under the same reaction conditions as those of Eq. (18) resulted in no reaction. The addition of additives such as AgClO_4 and *tmeda* or *dppb* improved the reaction.



$\text{IrCl}(\text{cod})_2/\text{AgClO}_4, \text{ tmeda}$	5 h	64% (100/0)
$\text{IrCl}(\text{cod})_2/\text{AgClO}_4, \text{ dppb}$	3 h	83% (0/100)



Scheme 2.5-23. Skeletal reorganization by GaCl₃.



Scheme 2.5-24. Enyne metathesis using [RuCl₂(p-cymene)]₂.

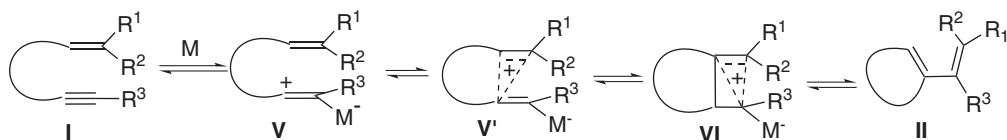
Very recently, the same group reported skeletal reorganization of enynes to 1-vinylcycloalkene catalyzed by GaCl₃ [2c].

The reaction proceeds in toluene at 0 °C and is completed within 1 h.

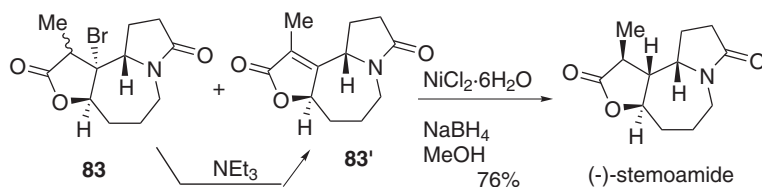
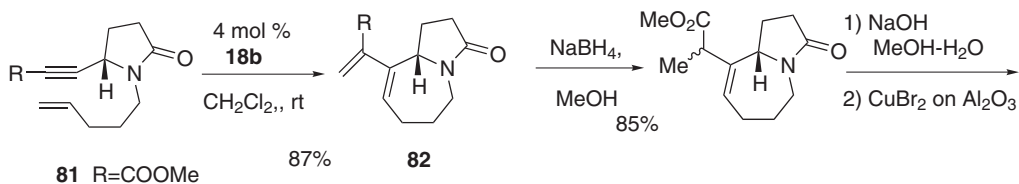
Dixneuf reported metathesis of 1,6-enyne **78** using [RuCl₂(p-cymene)]₂ in the presence of imidazolium salt and Cs₂CO₃ and obtained vinylcycloalkene **79** [27]. In this reaction, heterocyclic carbene would be generated and it coordinates to ruthenium catalyst.

Presumably, each skeletal reorganization reaction starts by coordination of the metal to the alkyne part, and then the alkene part attacks the cation center of the alkyne coordinated by metals.

However, the reaction mechanism is still not clear, and it is thought that the each reaction mechanism differs depending on the metal used.



Scheme 2.5-25. Reaction course of skeletal reorganization.



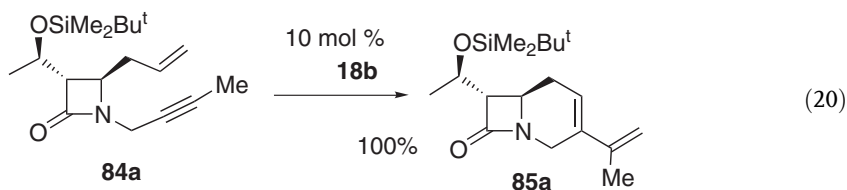
Scheme 2.5-26. Total synthesis of (-)-stemoamide.

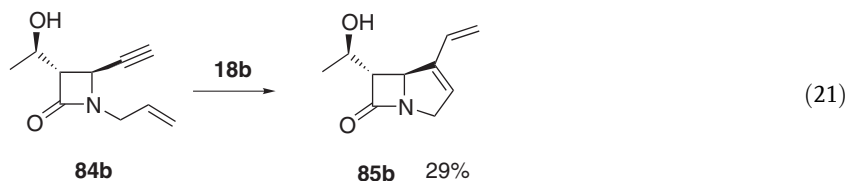
2.5.4

Utilization of Enyne Metathesis for the Synthesis of Natural Products and Related Biologically Active Substances

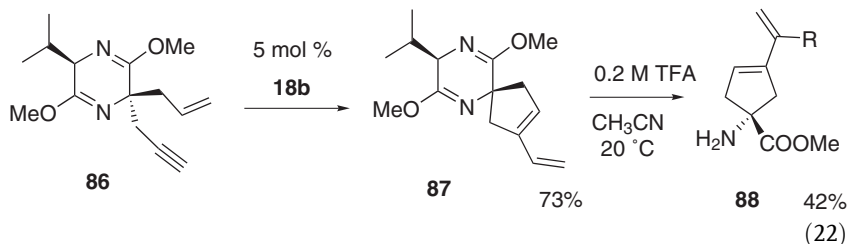
Because enyne metathesis has been developed recently, there are not many reports on the utilization of enyne metathesis in the syntheses of natural products and related compounds. The first report of the synthesis of a natural product using RCM is that by Mori, who succeeded in the total synthesis of (-)-stemoamide [28]. RCM of enyne **81**, which was obtained from (-)-pyroglutamic acid, using 4 mol% of **18b** afforded **82** in high yield. Reduction of the olefin followed by hydrolysis and then halolactonization afforded compounds **83** and **83'**. The latter compound **83'** was converted into (-)-stemoamide.

Barrett synthesized bicyclic β -lactams using RCM of enyne and obtained carba-cephem **84a** in high yield (Eq. (20)) [29a]. Later, a carbapenem skeleton was constructed in a similar manner, but the yield was low in this case (Eq. (21)) [29b].

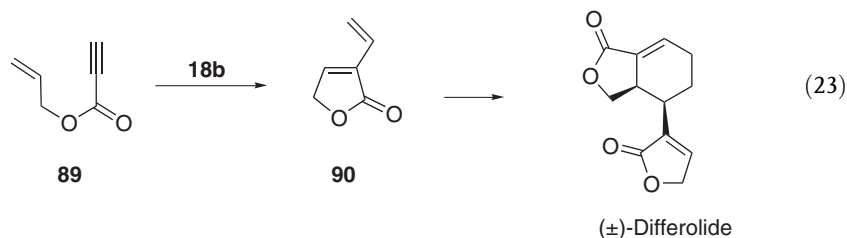




Undheim described the stereoselective synthesis of cyclic 1-amino-1-carboxylic acid **88** using ruthenium-catalyzed RCM (Eq. (22)) [30].



(±)-Differolide was synthesized by dimerization of 2-vinylbutenolide **90**, which was synthesized by enyne metathesis of allylpropynoate **89** [31].

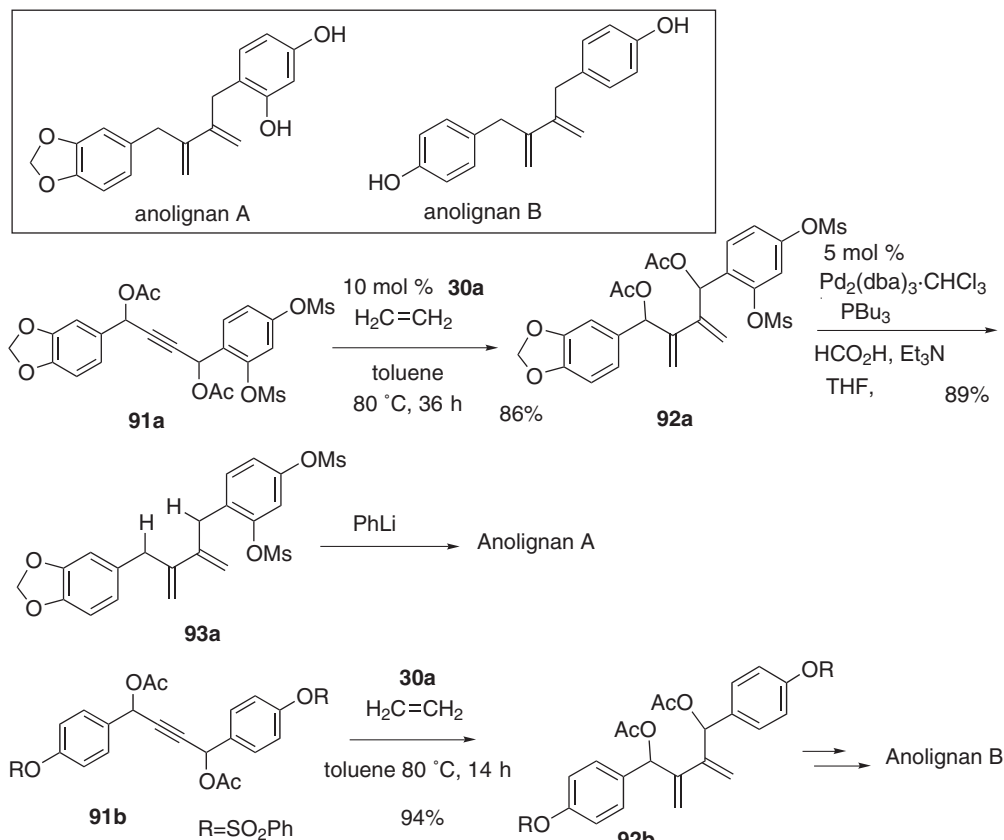


Total syntheses of anolignane A and anolignane B were achieved using cross enyne metathesis [32]. Treatment of alkyne **91a** with **30a** afforded 1,3-diene **92a** in high yield. Anolignane A was synthesized from **92a**. In a similar manner, **91b** afforded **92b** in high yield. Anolignane B was synthesized from **92b**.

Fürstner achieved formal total syntheses of the antibiotics metacycloprodigiosin and streptorubin B by platinum-catalyzed enyne metathesis reactions [33]. The key step to their metabridged pyrrole core structures consists of a metathesis reaction of electron-deficient enyne **93** catalyzed by PtCl_2 . The skeletal reorganization products **94a** and **94b** were converted into the respective target molecules.

Trost succeeded in the formal total synthesis of roseophilin. Macrocyclic compound **101** was synthesized from **100** by a platinum-catalyzed skeletal reorganization reaction, and it was then converted into **102**. Pyrrole derivative **99** was obtained from **102** [34].

Very recently, Shair succeeded in an ingenious total synthesis of (–)-longithorone from **104** and **106** [35].



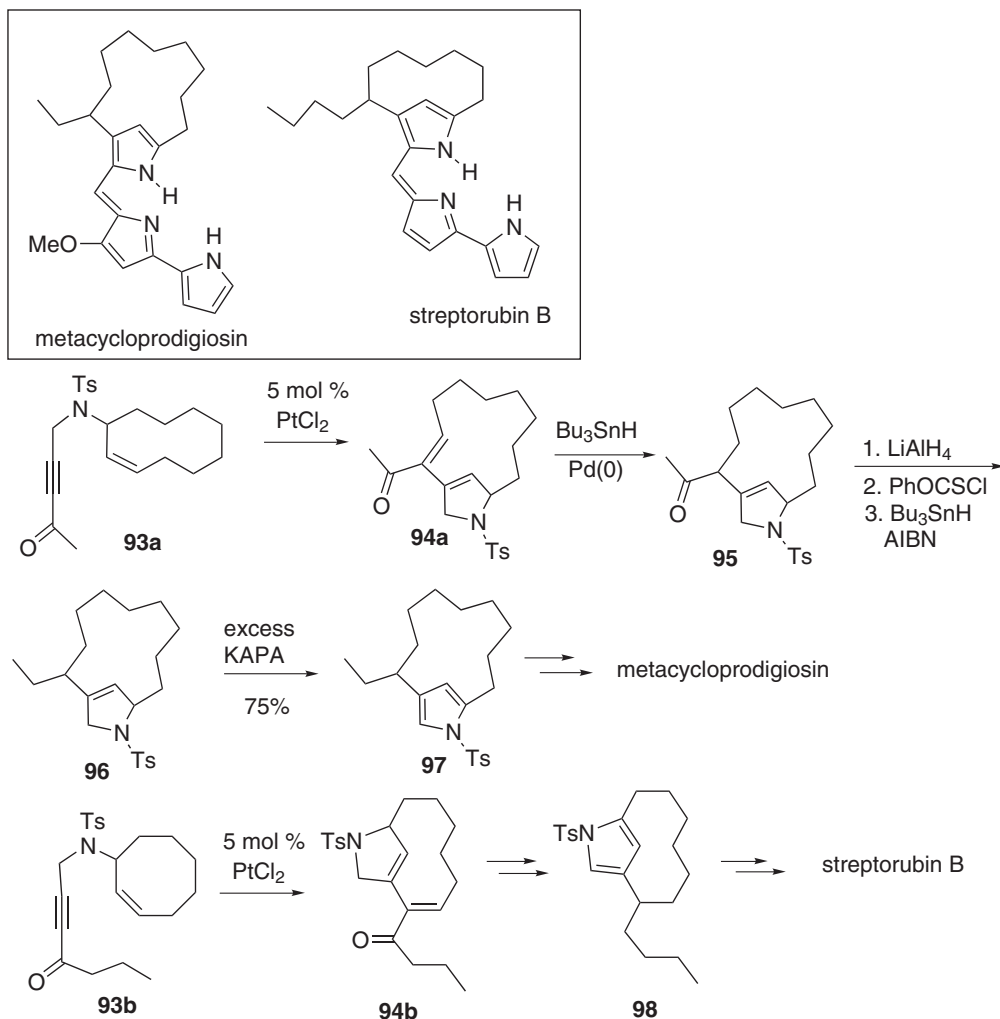
Scheme 2.5-27. Total syntheses of anolignan A and anolignan B.

These compounds were synthesized from **103** and **105** by ring-closing enyne metatheses under ethylene gas.

2.5.5

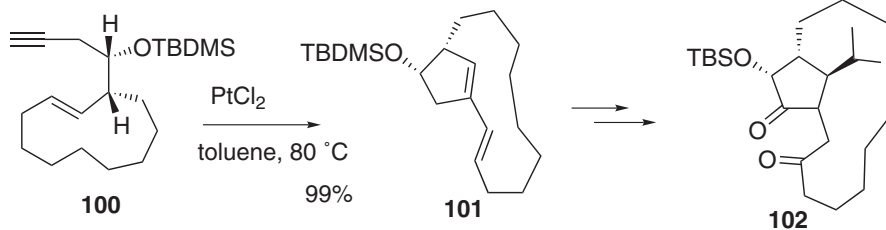
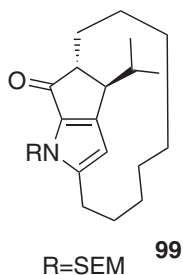
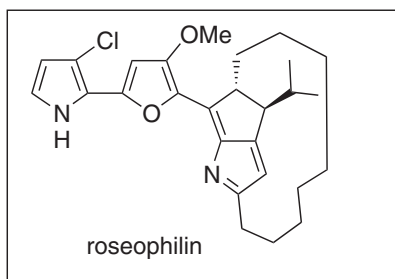
Perspective

Since the discovery of enyne metathesis by Katz in 1985, a wide range of enyne metathesis using various transition metals have been reported, and GaCl_3 -catalyzed skeletal reorganization has recently been discovered. The remarkable features of these reactions are that double and triple bonds are cleaved and that each alkylidene part of the alkene part is introduced onto the alkyne carbons to form the diene moiety. These reactions are very interesting, but there are not many

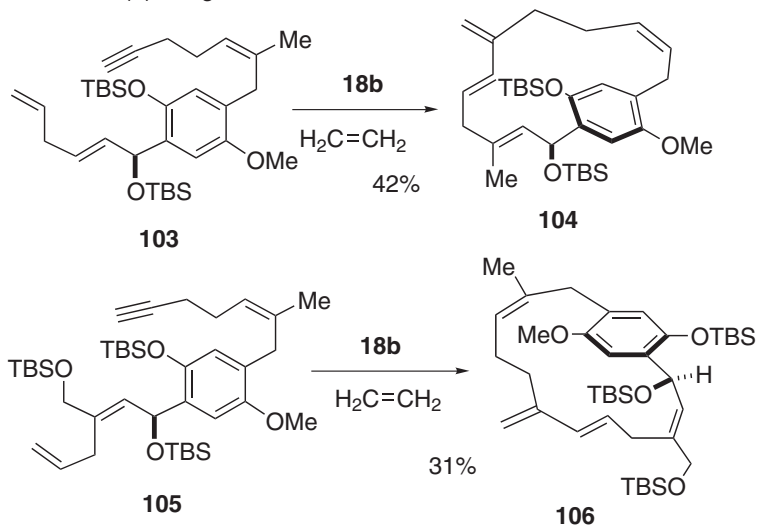
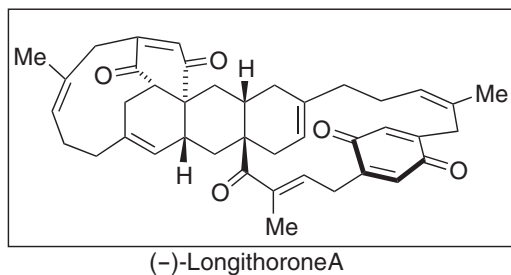


Scheme 2.5-28. Formal total syntheses of streptorubin B and metacycloprodigiosin.

reports for applications of enyne metathesis in synthetic organic chemistry because it is not so easy decide the structure of the starting material from that of an objective compound when enyne metathesis is used for the synthesis of complicated molecules, compared with that in the case of olefin metathesis (e.g., ROM-RCM or CM). Despite this difficulty, enyne metathesis should be used in the future for the syntheses of various complex molecules and macrocyclic compounds because the complicated molecules should be formed by one step, the reaction procedure is very simple, the yields are high, and the transition metal carbene complexes are now commercially available.



Scheme 2.5-29. Formal total synthesis of roseophilin.



Scheme 2.5-30. Total synthesis of (-)-longithorone A.

References

- 1 MORI, M. *Topics in Organometallic Chemistry*, Ed. FÜRSTNER, A. Springer-Verlag, Berlin, Heidenberg, **1998**, Vol 1, 133.
- 2 (a) CHATANI, N.; MORIMOTO, T.; MUTO, T.; MURAI, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. (b) CHATANI, N.; KATAOKA, K.; MURAI, M. *J. Am. Chem. Soc.* **1998**, *120*, 9104. (c) CHATANI, N.; INOUE, H.; KOTSUMA, H.; MURAI, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294.
- 3 (a) TROST, B. M.; TANOURY, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (b) TROST, B. M.; CHANG, V. K. *Synthesis*, **1993**, 824.
- 4 KATZ, T. J.; SIVAVEC, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737.
- 5 (a) MORI, M.; WATANUKI, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082. (b) WATANUKI, S.; OCHIFUJI, N.; MORI, M. *Organometallics* **1994**, *13*, 4129.
- 6 (a) SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) GRUBBS, R. H.; CHANG, S. *Tetrahedron*, **1998**, *54*, 4413. (c) KIM, S. H.; BOWDEN, N. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801. (d) KIM, S. H.; ZUERCHER, W. J.; BOWDEN, N. B.; GRUBBS, R. H. *J. Org. Chem.* **1996**, *61*, 1073.
- 7 SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DIMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
- 8 (a) KINOSHITA, A.; MORI, M. *Synlett* **1994**, 1020. (b) MORI, M.; SAKAKIBARA, N.; KINOSHITA, A. *J. Org. Chem.* **1998**, *63*, 6082. (c) KINOSHITA, A.; SAKAKIBARA, N.; MORI, M. *Tetrahedron* **1999**, *55*, 8155. (d) MORI, M.; KITAMURA, T.; SAKAKIBARA, N.; SATO, Y. *Org. Lett.* **2000**, *2*, 543. (e) MORI, M.; KITAMURA, T.; SATO, Y. *Synthesis* **2001**, 654.
- 9 CLARK, J. S.; TREVITT, P.; BOYALL, D.; STAMMEN, B. *Chem. Commun.* **1998**, 2629.
- 10 RENAUD, J.; GRAF, C.-D.; OBERER, L. *Angew. Chem. Int. Ed.* **2000**, *39*, 3101.
- 11 For **29a** see; (a) WESKAMP, T.; SCHATTENMANN, W. C.; SPIEGLER, M.; HERRMANN, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. For **29b** see; (b) HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSON, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (d) SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. For **30a** see; (e) SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953.
- 12 For a recent review, TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
- 13 (a) KITAMURA, T.; SATO, Y.; MORI, M. *Chem. Commun.* **2001**, 1258. (b) KITAMURA, T.; SATO, Y.; MORI, M. *Adv. Synth. Catal.* **2002**, *344*, 678.
- 14 SCHRAMM, M. P.; REDDY, D. S.; KOZMIN, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4274.
- 15 SAITO, N.; SATO, Y.; MORI, M. *Org. Lett.* **2002**, *4*, 803.
- 16 (a) KITAMURA, T.; MORI, M. *Org. Lett.* **2001**, *3*, 1161. (b) MORI, M.; KUZUBA, Y.; KITAMURA, T.; SATO, Y. *Org. Lett.* **2002**, *inpress*.
- 17 (a) RANDL, S.; LUCAS, N.; CONNON, S. J.; BLECHERT, S. *Adv. Synth. Catal.* **2002**, *344*, 631. (b) RÜCKERT, A.; EISELE, D.; BLECHERT, S. *Tetrahedron Lett.* **2001**, *42*, 5245.
- 18 (a) BANTI, D.; NORTH, M. *Tetrahedron Lett.* **2002**, *43*, 1561. (b) BANTI, D.; NORTH, M. *Adv. Synth. Catal.* **2002**, *344*, 694.
- 19 (a) A. KINOSHITA, N. SAKAKIBARA, M. MORI, *J. Am. Chem. Soc.* **1997**, *119*, 12388. (b) TONOGAKI, K.; MORI, M. *Tetrahedron Lett.* **2002**, 2235. (c) SMULIK, J. A.; DIVER, S. T. *Org. Lett.* **2000**, *2*, 2271.
- 20 (a) STRAGIES, R.; SCHUSTER, M.; BLECHERT, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 2518. (b) SCHÜRER, S. C.; BLECHERT, S. *Synlett*, **1998**, 166. (c) SCHÜRER, S. C.; BLECHERT, S. *Tetrahedron Lett.* **1999**, *40*, 1877.
- 21 MICALIZIO, G.; SCHREIBER, S. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 152.

- 22 SMULIK, J. A.; DIVER, S. T. *Tetrahedron Lett.* **2001**, 42, 171.
- 23 CHATANI, N.; FURUKAWA, N.; SAKURAI, H.; MURAI, S. *Organometallics*, **1996**, 15, 901.
- 24 OI, S.; TSUKAMOTO, I.; MIYANO, S.; INOUE, Y. *Organometallics*, **2001**, 20, 3704.
- 25 (a) FÜRSTNER, A.; SZILLAT, H.; STELZER, F. J. *Am. Chem. Soc.* **2000**, 122, 6785. (b) FÜRSTNER, A.; STELZER, F.; SZILLAT, H. *J. Am. Chem. Soc.* **2001**, 123, 11863.
- 26 CHATANI, N.; INOUE, H.; MORIMOTO, T.; MUTO, T.; MURAI, S. *J. Org. Chem.* **2001**, 66, 4433.
- 27 (a) ACKERMANN, L.; BRUNEAU, C.; DIXNEUF, P. H. *Synlett*, **2001**, 397. (b) SEMERIL, D.; BRUNEAU, C.; DIXNEUF, P. H. *Adv. Synth. Catal.* **2002**, 344, 585.
- 28 (a) KINOSHITA, A.; MORI, M. *J. Org. Chem.* **1996**, 61, 8356. (b) KINOSHITA, A.; MORI, M. *Heterocycles* **1997**, 46, 287.
- 29 (a) BARRETT, A. G. M.; BAUGH, S. P. D.; BRADDOCK, D. C.; FLACK, K.; GIBSON, V. C.; PROCOPIOU, P. A.; WHITE, A. J. P.; WILLIAMS, D. J. *J. Org. Chem.* **1998**, 63, 7893. (b) DUBOC, R.; HENAUT, C.; SAVIGNAC, M.; GENET, J.-P.; BHATNAGAR, N. *Tetrahedron Lett.* **2001**, 42, 2461.
- 30 (a) HAMMER, K.; UNDEHEIM, K. *Tetrahedron.* **1997**, 53, 10603. (b) KOTHA, S.; SREENIVASACHARY, N.; BRAHMACHARY, *Eur. J. Org. Chem.* **2001**, 787.
- 31 HOYE, T. R.; DONALDSON, S. M.; VOS, T. J. *Org. Lett.* **1999**, 2, 277.
- 32 M. MORI, K. TONOGAKI, N. NISHIGUCHI, *J. Org. Chem.* **2002**, 67, 224.
- 33 FÜRSTNER, A.; SZILLAT, H.; GABOR, B.; MYNOTT, R. *J. Am. Chem. Soc.* **1998**, 120, 8305.
- 34 TROST, B. M.; DOHERTY, G. A. *J. Am. Chem. Soc.* **2000**, 122, 3801.
- 35 LYATON, M. E.; MORALES, C. A.; SHAIR, M. D. *J. Am. Chem. Soc.* **2002**, 124, 773.

2.6

Ring-Opening Cross-Metatheses

Thomas O. Schrader and Marc L. Snapper

2.6.1

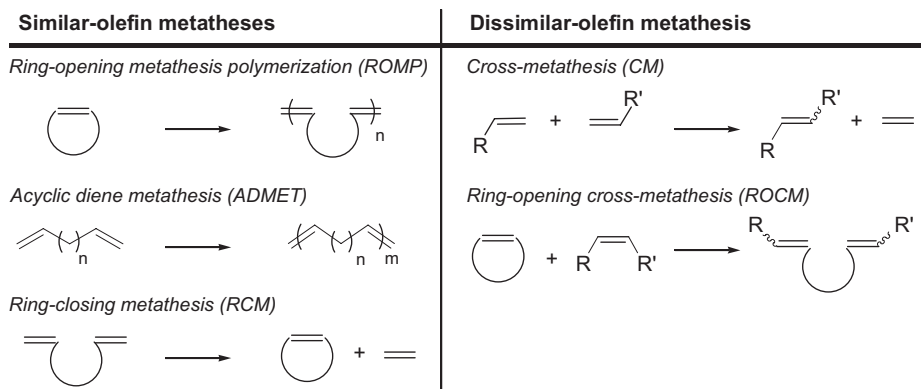
Introduction

With the remarkable utility of ring-closing metathesis (RCM) and ring-opening metathesis polymerizations (ROMP) clearly recognized [1], it is of some interest that other variants of olefin metatheses, such as cross-metatheses (CM) [2] and ring-opening cross-metatheses (ROCM) have received considerably less attention from the synthetic organic community. This can be understood, in part, by the additional selectivity necessary for controlled reactions between the dissimilar olefins in these intermolecular processes (Scheme 2.6-1). Nonetheless, ROCM and CM have begun to emerge within the last decade as unique and powerful methods for the efficient construction of molecular targets.

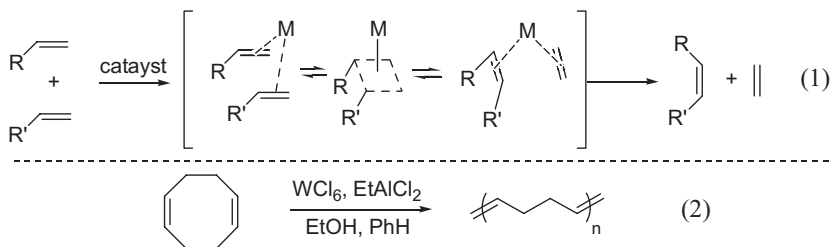
Cross-metathesis involves the intermolecular exchange of olefin components (alkylidenes) between two different acyclic olefins. Often the release of ethylene or another volatile olefin drives the selective cross-metathesis to completion. In ring-opening cross-metathesis, a variant of cross-metathesis, there is an intermolecular exchange between a cyclic olefin and an acyclic olefin. In this case, release of ring strain in the cyclic olefin has been used most frequently to propel the transformation.

The emergence of ROCM as a valuable tool for the synthetic organic chemist coincides with the availability of well-defined, substrate tolerant, and user-friendly catalytic systems to promote olefin metathesis [3]. The recent success and development of these new intermolecular olefin metatheses can be attributed perhaps to the attenuated reactivity and greater selectivity exhibited by the newer, well-defined metathesis-active complexes.

Given the prominent role of ROCM in the evolution of our understanding of the mechanism of olefin metatheses, this chapter begins with early examples of the intermolecular transformation. It will then be followed by the introduction of modern ROCM methods, arising from the introduction of structurally well-defined metathesis active systems. The chapter concludes with an overview of recent applications of ROCM in the efficient synthesis of natural product targets.



Scheme 2.6-1. Selective olefin metatheses for similar and dissimilar olefins.



Scheme 2.6-2. Pair-wise mechanism for metathesis.

2.6.2

Early Examples of ROCM

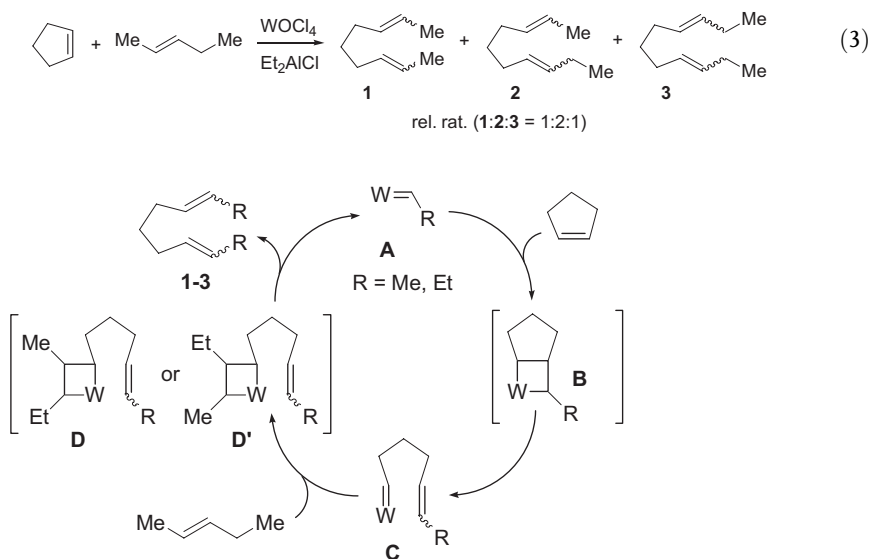
2.6.2.1

Mechanistic Insight

Early examples of ROCM were low yielding and proceeded with little selectivity; however, these reactions did provide key insight into the mechanism of the olefin metathesis process. In the course of studying the polymerization of cyclic olefins using a tungsten-based catalyst system [4], Calderon observed low-molecular-weight products that could not be explained readily by the previously proposed “pair-wise” metathesis mechanism (Eq. (1), Scheme 2.6-2) [5]. For example, during the polymerization of 1,5-cyclooctadiene, products containing the same repeat unit ($\text{=CH-CH}_2\text{-CH}_2\text{CH=}$) were observed (Eq. (2)). Because the pair-wise mechanism predicts that oligomers would contain multiples of monomer units (i.e., $n \times m$ units, where n is an integer), the observed products must have arisen from an alternative pathway [6].

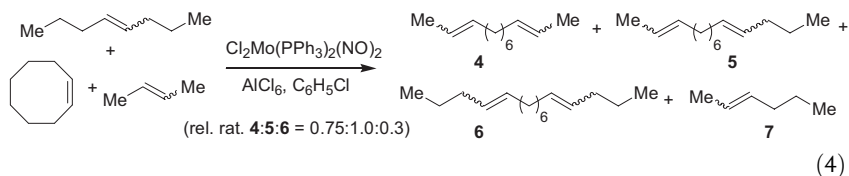
Chauvin and coworkers provided further evidence against the pair-wise mechanism [7]. In the ROCM of cyclopentene with 2-pentene, Chauvin observed dienes 1, 2, and 3 in a statistical distribution ($1:2:3 = 1:2:1$, Eq. (3)). Using the pair-wise mechanism, only diene 2 would be expected at low conversion [8]. As illustrated

in Scheme 2.6-3, Chauvin proposed the interchange of metal carbenes (also called alkylidenes) via metallocyclobutane intermediates as an alternative mechanism for olefin metathesis [9]. Tungsten alkylidene **A** reacts in a [2+2] fashion with 1 equivalent of cyclopentene to generate metallocyclobutane **B**. Retrocycloaddition from **B** produces the new tungsten alkylidene **C**, which reacts with 2-pentene to generate metallocyclobutane **D** or **D'**. Productive cleavage of the metallacycle (**D** or **D'**) gives the desired ring-opened product (**1**, **2**, or **3**) and regenerates the starting alkylidene (**A**), thus completing the catalytic cycle.



Scheme 2.6-3. Alkylidene mechanism in ROCM for olefin metathesis.

In 1975, Katz provided additional support for the Chauvin mechanism [10]. Treatment of cyclooctene with a mixture of 2-butene and 4-octene gave dienes **4**, **5**, **6**, and **7** at 5% cyclooctene consumption (rel. rat. **4**:**5**:**6** = 0.75:1.0:0.3, Eq. (4)). Due to the presence of diene **5**, these results could not be explained by the pair-wise mechanism.

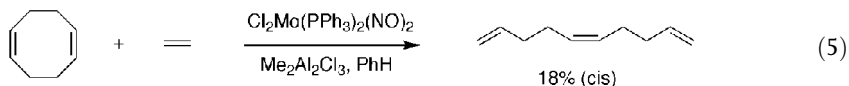


2.6.2.2

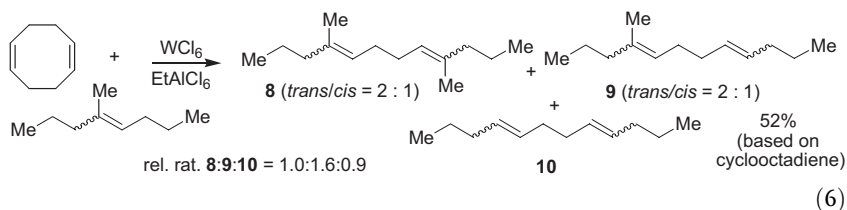
Early Efforts toward a Selective ROCM

In 1970, Zuech et al. reported the ring opening of 1,5-cyclooctadiene with ethylene (Eq. (5)) [12]. Infrared analysis of the product, 1,5,9-decatriene revealed a *cis*-

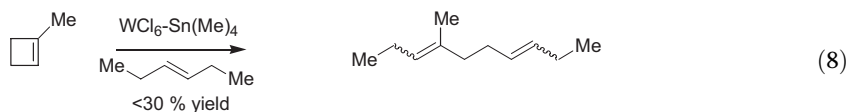
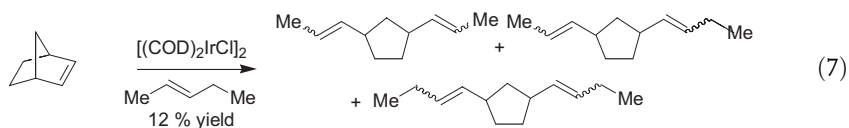
internal double bond, indicating that secondary cross-metathesis reactions were not responsible for the formation of the monomeric product.



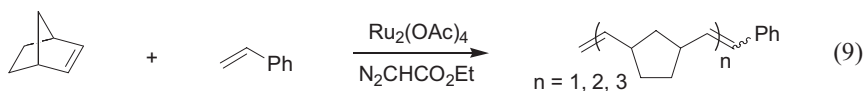
A ROCM of 1,5-cyclooctadiene with 4-methyl-4-octene was reported by Pinazzi et al. [13] to give dienes **8**, **9**, and **10** as a mixture of olefin isomers (rel. rat. **8:9:10** = 1.0:1.6:0.9, Eq. (6)). Interestingly, ^1H NMR analysis of products **8** and **9** revealed selective formation of the *trans* trisubstituted olefin isomers vs. the *cis* trisubstituted isomers ($\sim 2:1$, *trans:cis* for both **8** and **9**).



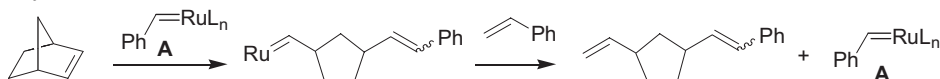
A few early examples of ring-opening cross-metathesis with more strained cyclic olefins gave monomeric products, albeit with little selectivity. ROCM of norbornene with *trans*-2-pentene using an iridium-based catalyst gave only 12% yield of desired products in a statistical distribution (Eq. (7)) [14]. Similarly, ring opening of 1-methyl-cyclobutene with *trans*-3-hexene gave monomeric products in less than 30% yield as a mixture of stereoisomers (Eq. (8)) [15].



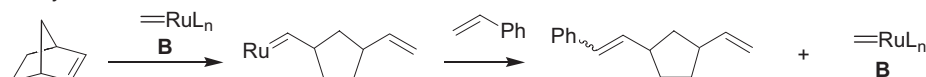
The ROCM of norbornene with styrene was also reported using a ruthenium-based catalyst to give unsymmetrical products as a mixture of monomers and oligomers (Eq. (9)) [16]. This represents an early example of a selective ROCM process, suggesting that the formation of particular metal alkylidenes is likely favored. As shown in Scheme 2.6-4, if alkylidene **A** is preferred, the styrenyl unit is transferred initially to generate an alkylidene derived from the cyclic olefin. This is then followed by addition of the methylene substituent from styrene to reform alkylidene **A**. Alternatively, the methyldiene **B** could be one of the propagating complexes,



Alkylidene favored mechanism:



Methylidene favored mechanism:



Scheme 2.6-4. A selective ROCM process.

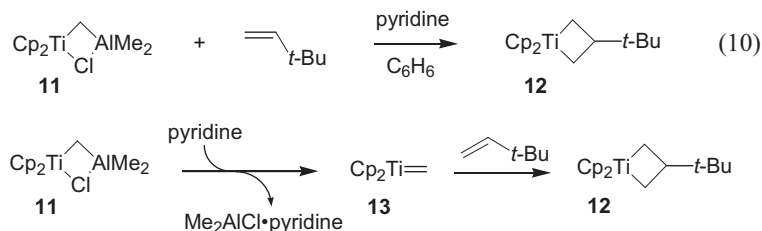
which upon reaction with norbornene, followed by addition of the styrene, regenerate methylidene **B**. In either case, it will be the reactivity preferences of the two alternating metal alkylidenes generated in the ROCM that lead to a selective cross-metathesis process.

2.6.2.3

Well-Defined Metal Complexes as Catalysts

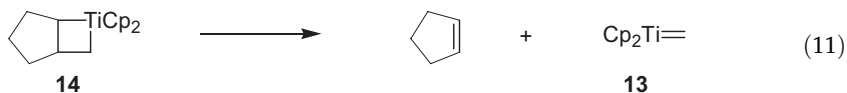
In 1978, Tebbe and Parshall [17] reported that titanium-complex **11**, “Tebbe’s reagent,” catalyzed the degenerate metathesis of isobutene. In 1980, Grubbs [18] found that treatment of the titanium complex **11** with pyridine in the presence of neohexene, resulted in the formation of titanacyclobutane **12** as a stable, isolable compound (Eq. (10), Scheme 2.6-5). This experiment suggested the role of the co-catalyst (11) in the metathesis reaction. Pyridine liberates Me_2AlCl and a reactive $[\text{Cp}_2\text{Ti}=\text{CH}_2]$ fragment **13** that is trapped immediately by the olefin to form titanacyclobutane **12**. These experiments demonstrated clearly the role of metallacycles and carbenes in the olefin metathesis reaction, thereby giving credence to the non-pair-wise mechanism postulated by Chauvin.

Although methylidene **13** effectively catalyzed degenerate metathesis reactions, the ability of **13** to catalyze the productive metathesis of 1,2-disubstituted olefins had proven difficult [19]. For example, thermolysis of metallacycle **14**, derived from the cycloaddition of **13** with cyclopentene, quantitatively regenerated **13** and cyclo-

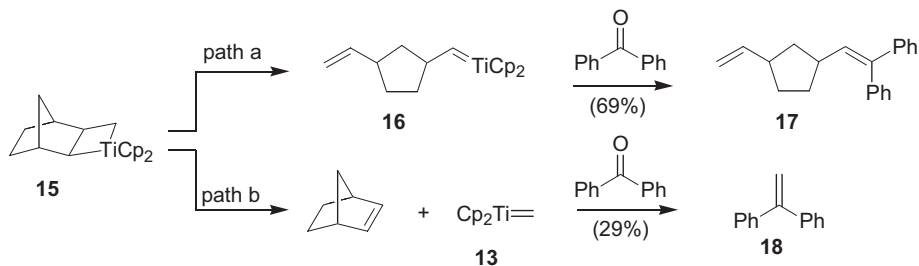


Scheme 2.6-5. Tebbe’s reagent.

pentene (Eq. (11)). This indicated the prevalent pathway for dissociation of compound **14** was the reverse of its formation.

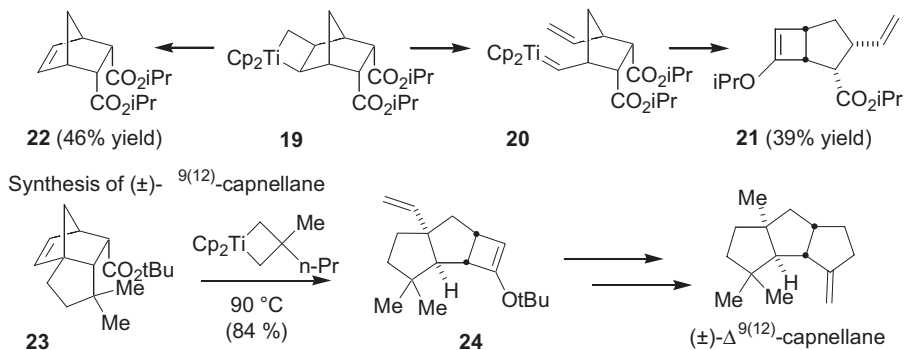


To circumvent this issue, metallacycle **15** was prepared via the addition of **13** with norbornene (Scheme 2.6-6) [20]. Due to the ring strain associated with norbornene (27 kcal mol⁻¹), it was postulated that upon thermolysis, the new alkylidene **16** would be preferred (path a) over the unproductive pathway (path b). Indeed, thermolysis **15** in the presence of benzophenone, to trap the resultant alkylidenes (**16** and **13**), gave 69% of the ring-opened product **17** and 29% 1,1-diphenylethylene (**18**).

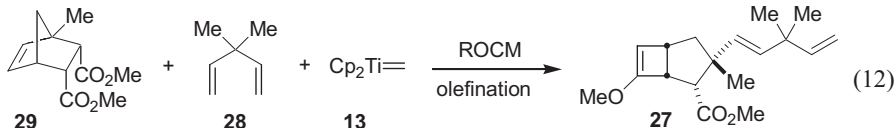


Scheme 2.6-6. Ring-opening metathesis with Tebbe's reagent.

The selective ring-opening olefination process was examined further using metallacycle **19** (Scheme 2.6-7). The ester acts as an intramolecular trap for the alkylidene (**20**), formed from the thermolysis of **19**, to produce cyclobutene **21** in 39% yield along with 46% yield of recovered bis-ester **22**. This methodology was utilized effectively in the total synthesis of the triquinane, (±)-Δ⁹⁽¹²⁾-capnellane, where compound **23** was rearranged in 84% yield to cyclobutene **24**, which was then carried on to the natural product [21].



Scheme 2.6-7. Ring-opening intramolecular trapping: Synthesis of (±)-Δ⁹⁽¹²⁾-capnellane.

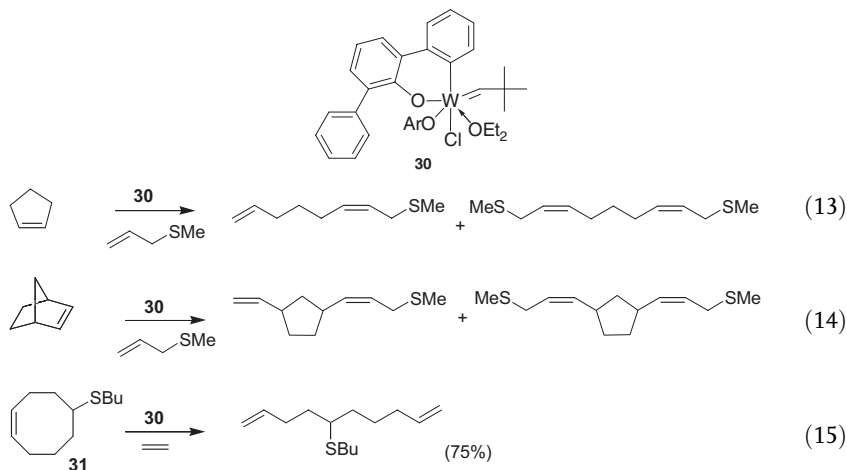


Scheme 2.6-8. Ring-opening cross-metathesis with Tebbe's reagent.

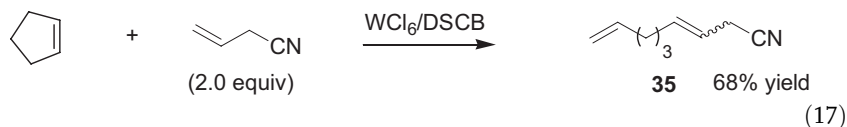
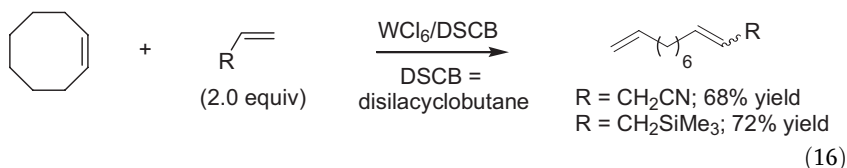
Grubbs also demonstrated the use of alkylidene **13** in a ROCM/olefination reaction (Scheme 2.6-8). Using titanacycle **25** (obtained from the addition of **13** to 3,3-dimethylcyclopropene) as a source of alkylidene **26**, compound **27** was formed via ring opening of norbornene **29** and subsequent intramolecular olefination. This represents a formal ring-opening cross-metathesis (ROCM) of diene **28** and norbornene **29** (Eq. (12)).

While Tebbe's reagent (**11**) promoted the ring opening of norbornyl substrates, these reactions terminated in the formation of the stable titanium-oxo species $\text{Cp}_2\text{Ti}=\text{O}$. This necessitates that the reaction be stoichiometric with respect to the titanium complex. A more practical and cost-effective solution would be to use in sub-stoichiometric amounts a well-defined metal complex that can catalyze the ROCM process.

Along these lines, Basset and coworkers demonstrated the use of an isolable tungsten alkylidene **30** as a catalyst for ROCM [22]. The ROCM reactions of both cyclopentene and norbornene with allyl methyl sulfide were catalyzed by complex **30** (Eqs. (13) and (14), no yields reported). In addition, alkylidene **30** also promoted the ring opening of 4-*n*-butyl-thiocyclooctene **31** with ethylene in appreciable yield (75%, Eq. (15)).



Another early example of an efficient and selective ring-opening cross-metathesis was reported by Bespalova et al. [23]. The ROCM of cyclooctene with terminal olefins, using a WCl_6 /1,1,3,3-tetramethyl-1,3-disilacyclobutane co-catalyst system, formed acyclic substituted 1,9-dienes in a synthetically useful yield (Eq. (16)). In addition, a ROCM of cyclopentene with allylnitrile was accomplished to give diene **35** in 68% yield (Eq. (17)). Considering the tendency to form 5-membered rings through RCM, the efficiency of this ROCM process is unexpectedly high.



2.6.2.4

New Opportunities for Olefin Metathesis

The introduction of the new, structurally defined, highly accessible metathesis pre-catalysts **32**, **33**, and **34** (Figure 2.6-1) has undoubtedly been responsible for the considerable attention that olefin metathesis has received in the last decade. The molybdenum-based complex **32** (Schrock catalyst), introduced by the Schrock group in 1990 [24], and the ruthenium-based complexes **33** and **34** (Grubbs' catalyst) [25], synthesized in the laboratories of R. H. Grubbs in 1993 and 1995, respectively [26], have demonstrated excellent utility for all types of olefin metathesis reactions. It is the availability of these metathesis-active complexes that has allowed for the introduction and development of the selective and efficient ROCM processes that will be discussed in the remainder of this chapter.

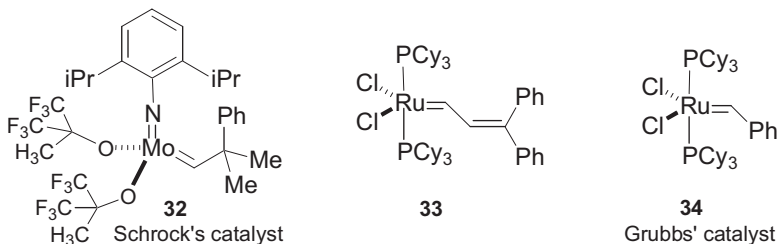


Fig. 2.6-1. Modern olefin metathesis catalysts.

2.6.3







Selective ROCM Reactions

2.6.3.1

ROCM Involving Cyclobutenes

Several examples of chemoselective ROCM involve the use of strained cycloolefins to facilitate the ring-opening process (Table 2.6-1). Work in our laboratories has focused on the ROCM of cyclobutene-containing compounds with terminal olefins. The catalytic ring-opening cross-metathesis of bicyclo[3.2.0]heptenes with various terminal olefins, using vinylidene catalyst **33**, was reported in 1995 (Table 2.6-2) [27]. Generally, the *Z*-configuration for the newly formed 1,2-disubstituted olefin was favored.

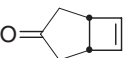
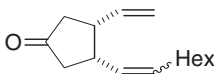

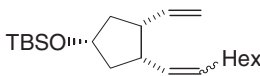

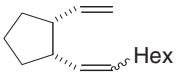

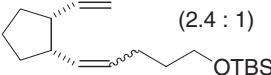
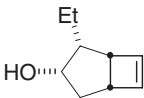
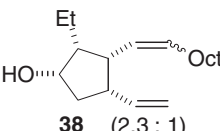
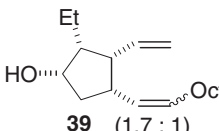

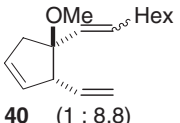
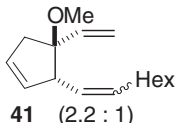
Tab. 2.6-1. Strain energies of selected cyclic olefins.

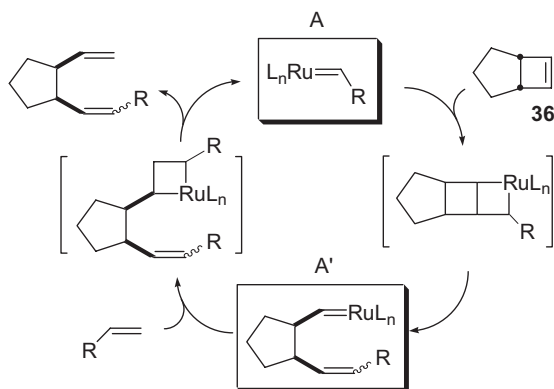
Olefin	Strain energy, ΔH°_f 298 (kcal/mol)	Olefin	Strain energy, ΔH°_f 298 (kcal/mol)
	53.7		1.4
	29.8		6.0
	5.9		27.2

Values taken from: Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry* 3rd edition; Harper Collins Publishers: New York, 1987, Chapter 2.

A deuterium crossover experiment was carried out to explore the mechanism of the ROCM in this series. The ROCM of cyclobutene **36** with an equal mixture of $\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{OTBS}$ and $\text{CH}(\text{D})=\text{CD}(\text{CH}_2)_3\text{OTBS}$ generated at low conversion a relatively substantial number of monodeuterated products (Eq. (18)). Furthermore, the recovered monosubstituted olefins did not appear to scramble their initial deuterium/hydrogen composition. These results are consistent with an alternating alkylidene mechanism, where the alkylidene generated from the terminal olefin (A) reacts with the strained cyclobutene (**36**), and the more hindered alkylidene generated from the opening of the cyclobutene (A') reacts preferentially with the least hindered olefin in the reaction (Scheme 2.6-9). Also of possible significance is the larger fraction of non-deuterated terminal olefin incorporated into the ring-

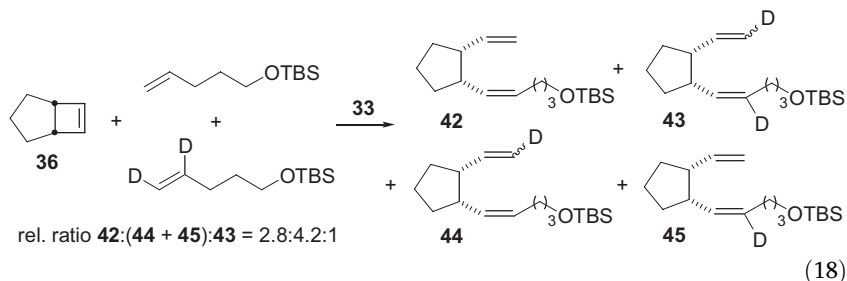
Tab. 2.6-2. ROCM of bicyclo[3.2.0]heptenes with monosubstituted olefins using catalyst **33**.

Entry	Cycloolefin	Terminal olefin	Products (Z:E)	Isolated yields
(1)		1-octene	 (2.3 : 1)	63%
(2)	TBSO- 	1-octene	TBSO-  (2.2 : 1)	69%
(3)	36 	1-octene	 (3.2 : 1)	68%
(4)	36 	TBS-4-penten-1-ol	 (2.4 : 1)	46%
(5)	Et- 	1-decene	Et-  (2.3 : 1) 38 Et-  (1.7 : 1) 39	56% 38:39 1.3:1.0
(6)	OMe- 	1-octene	OMe-  (1 : 8.8) 40 OMe-  (2.2 : 1) 41	81% 40:41 4.1:1.0

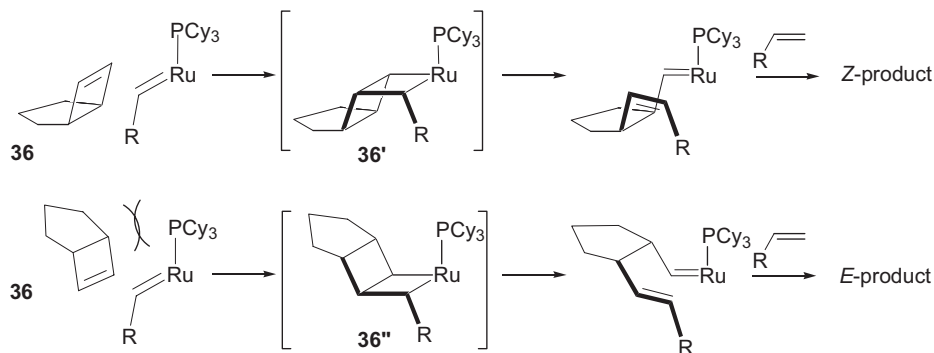


Scheme 2.6-9. Selective ROCM through alternating alkylidene mechanism.

opened product versus deuterated material. If the preference for consumption of non-deuterated terminal olefin arises from secondary isotope effects, one would expect the fragmentation of one of the metallocyclobutanes as the rate-limiting step in this mechanism.

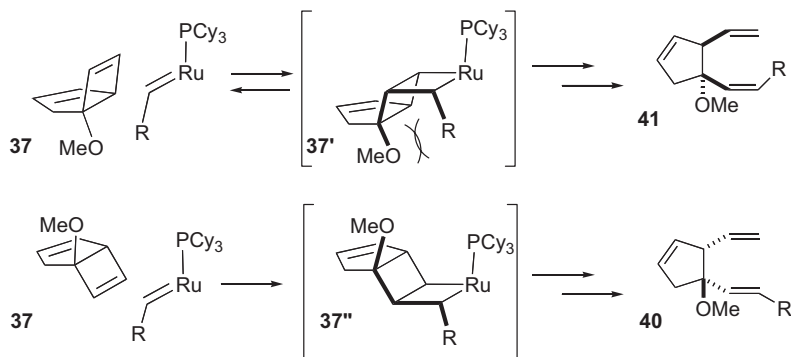


A model for the observed *Z*-olefin selectivity is proposed in Scheme 2.6-10. Cyclobutene **36** prefers to approach to the alkylidene away from the bulky tricyclohexylphosphine ligand favoring the formation of metallocyclobutane **36'** over **36''**. Fragmentation of complex **36'** provides the *Z*-olefin-containing product.



Scheme 2.6-10. Olefin stereoselectivity in ROCM.

A notable exception in the selectivity trends was observed in the ROCM cyclobutene **37** with 1-octene (Table 2.6-2, entry 6). Moderate regioselectivity (4:1 **40**:**41**) was observed in this reaction, favoring diene **40** over regioisomer **41**. In this case, a high degree of *E*-olefin selectivity was observed for the major regioisomer (**40**). This result can be rationalized by the model shown in Scheme 2.6-11. The major regioisomer **40** is formed by a cyclobutene approach that keeps the angular methoxy group found in cyclobutene **37** away from the bulky metal center. The usual approach of the cyclobutene is disfavored due to 1,3-interactions with the alkylidene group in metallocyclobutane **37'**. To avoid this interaction, the cyclobutene (**37**) now favors approach to the ruthenium toward the phosphine ligand (forming metallocyclobutane **37''**). The approach introduces selectivity a disubstituted *E*-olefin at the more substituted side of the product (**40**).

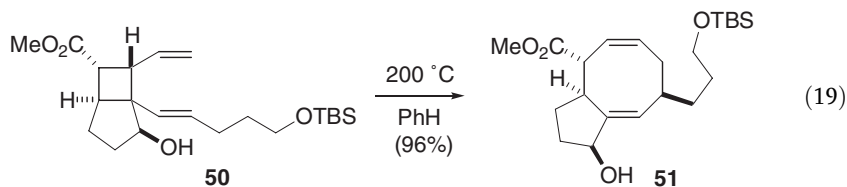


Scheme 2.6-11. Steric influence in regio- and stereoselective ROCM.

2.6.3.2

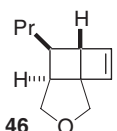
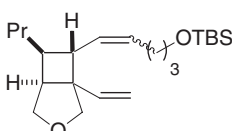
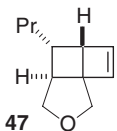
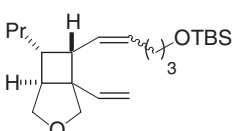
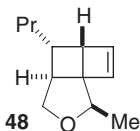
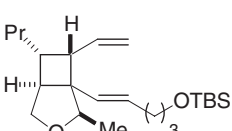
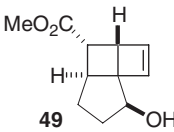
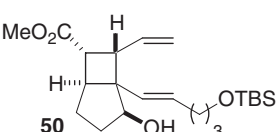
Regio- and Stereoselective ROCM

To enhance the regio- and stereoselectivity of ROCM processes involving cyclobutenes, the ROCM reactions of highly functionalized cyclobutene compounds with TBS-protected 4-penten-1-ol were investigated (Table 2.6-3) using pre-catalyst **34** (Figure 2.6-1) [28]. While the ROCM of cyclobutenes **46** and **47** with TBS-4-penten-1-ol gave ring-opened products with little regio- and stereoselectivity (entries 1 and 2), the ring-opening reactions of **48** and **49** provided products with appreciable levels of selectivity (entries 3 and 4). The major regioisomers formed in both cases were of the *E*-olefin geometry (>20:1). The efficacy of the selective ROCM processes was illustrated by the conversion of the metathesis products into bicyclo[6.3.0] ring systems. For example, ring-opened product **50** was heated to 200 °C to give cyclooctadiene compound **51** through a Cope rearrangement (Eq. (19)).



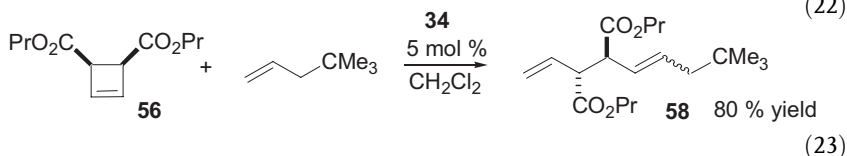
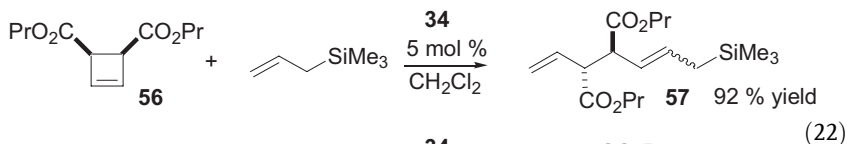
It is noteworthy that attempted ROCM reactions involving cyclobutene **52** (diastereomeric to compound **48** at the methyl group) and various terminal olefins failed to give the desired ring-opened products. Further studies showed that treatment of cyclobutene **52** with stoichiometric **34** resulted in the formation of a new alkylidene **53** (Eq. (20)) [29], which fails to react when excess styrene is introduced. Likewise, when cyclobutene **48** is reacted with one equivalent of Grubbs' catalyst (**34**), a new alkylidene **54** is also formed (Scheme 2.6-12). In this case, however, treatment of alkylidene **54** with styrene generates diene **55**, where the terminal

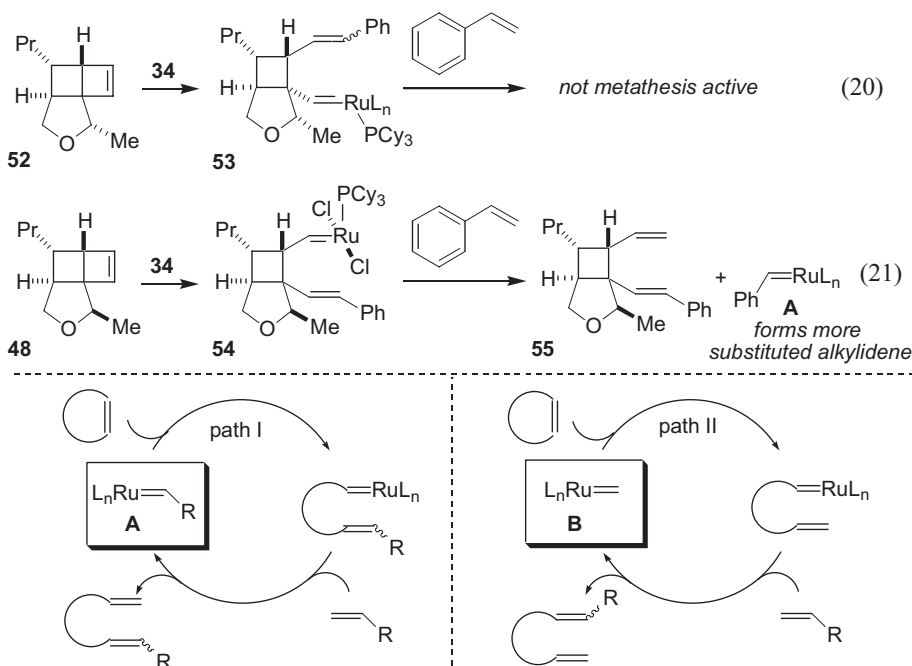
Tab. 2.6-3. ROCM of functionalized cyclobutenes with TBS-4-penten-1-ol.

Entry	Cyclobutene	Major product	Yield (regioisomer ratio)
(1)			84% (1.5:1)
(2)			76% (1.4:1)
(3)			72% (8:1)
(4)			60% (10:1)

carbon of styrene is transferred selectively to **54**, thereby generating the substituted alkylidene **A**. This experiment suggests that the active catalyst in the ROCM reaction is the substituted alkylidene **A**, not methyldiene **B** (Scheme 2.6-12, path I favored over path II).

Blechert and coworkers also demonstrated selective ROCM reactions involving cyclobutenes to give acyclic diene products (Eqs. (22) and (23)) [30]. ROCM of cyclobutene **56** with allyltrimethylsilane or 4,4-dimethylpentene, using catalyst **34**, provides acyclic dienes **57** and **58** in 92% and 80% yields, respectively.





Scheme 2.6-12. Monophosphine ruthenium catalyst: identity of the propagating alkylidene.

2.6.3.3

ROCM of Bridged Bicyclic Alkenes

Olefin metatheses involving bridged bicyclic alkenes constitute a large portion of the literature on selective ROCM. Much like cyclobutenes, these substrates allow for an efficient ROCM process due to the release of ring strain upon ring opening. In 1996, Blechert and coworkers reported the ROCM of 1,2-disubstituted olefins with norbornyl and 7-oxanorbornyl derivatives (Table 2.6-4) [31]. In order to suppress polymerization of the cycloolefin, the reactions were carried out in dilute solutions (max. 0.1 M) using 10-fold excess of the acyclic olefin. Moderate stereoselectivities were observed for the newly formed 1,2-disubstituted olefins. In all cases the *E,E*-isomer predominated over the *E,Z*-isomer.

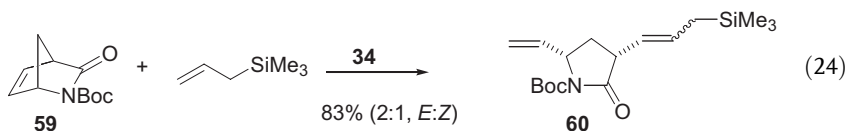
Additional selective ROCM reactions of norbornenes and 7-oxanorbornenes with terminal olefins have also been observed (Table 2.6-5) [32]. The reaction has been found to tolerate numerous functional groups including free alcohols (entries 3 and 8), silyl ethers (entries 4 and 5), silanes (entry 1), stannanes (entry 2), selenides (entry 9), nitriles (entry 4), anhydrides (entries 2 and 7), esters (entries 3, 8, and 9), and various substituted aromatics (entries 7 and 8). The generality of these ROCM reactions have allowed for the convenient preparation of a variety of highly substituted, unsymmetrical cyclopentane and tetrahydrofuran derivatives.

Tab. 2.6-4. ROCM Examples of bicyclic alkenes with 1,2-disubstituted olefins.^a


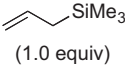
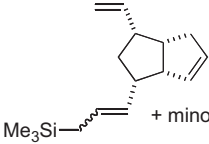
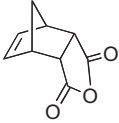
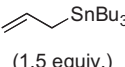
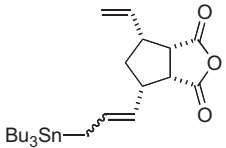
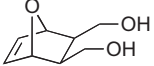
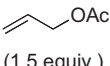
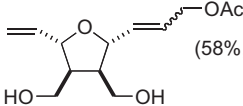
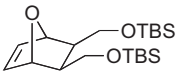
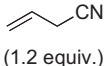
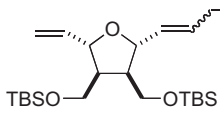
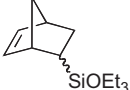

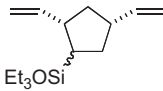


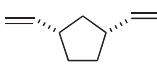
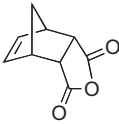
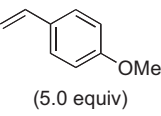
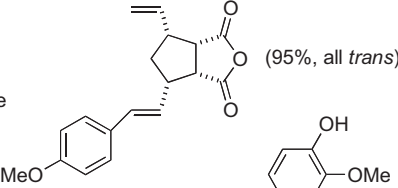
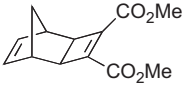
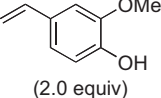
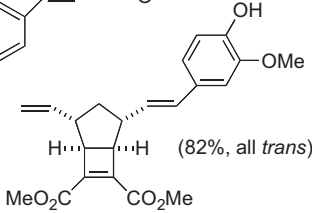
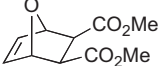

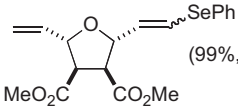
Entry	Cycloolefin	Acyclic olefin	Product	Yield (E, E:E, Z ratio)
(1)				68% (1.5:1)
(2)				94% (2:1)
(3)				85% (2:1)
(4)				73% (1.5:1)
(5)				89% (nd) ^b

^a Reactions typically carried out in benzene or CH₂Cl₂ using catalyst **33** or **34**. ^b Ratio not determined.

Regioselective ROCM has been observed in several cases involving bridged bicyclic alkenes. For instance, the ring opening of lactam **59** with trimethylallylsilane generates a single regioisomer **60** (Eq. (24)) [30]. Similarly, selectivity was observed in the ROCM of 2-substituted 7-oxanorbornenes with allyl acetate (Eq. (25)) [33]. When the ROCM of **61** with allyl acetate was run at higher concentration, the ring-opening dimerization/cross-metathesis pathway displayed excellent regioselectivity (Eq. (26)) [34].



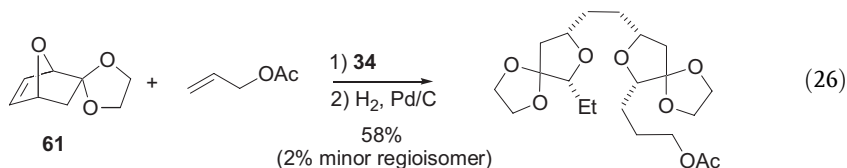
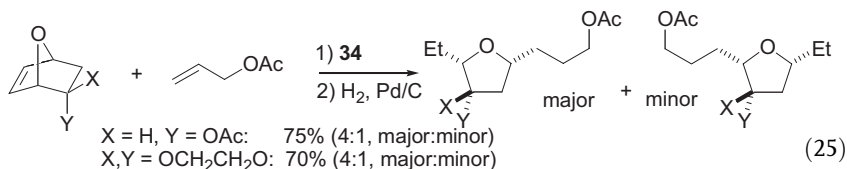
Tab. 2.6-5. Ring opening of norbornenes and 7-oxanorbornenes with terminal olefins.

Entry	Cycloolefin	Terminal olefin	Product (yield, E:Z ratio)	Ref.
(1) ^a		 (1.0 equiv)	 (94%, 5:1) + minor regioisomer ^c	30
(2) ^b		 (1.5 equiv.)	 (95%, 2:1)	30
(3) ^a		 (1.5 equiv.)	 (58%, 1:2)	30
(4) ^a		 (1.2 equiv.)	 (87%, 1:3)	30
(5) ^a		 (xs)	 (87%, 1:3)	32c
(6) ^a		 (5.7 equiv)	 (76%, 2.3:1)	29b
(7) ^a		 (5.0 equiv)	 (95%, all <i>trans</i>)	32a
(8) ^a		 (2.0 equiv)	 (82%, all <i>trans</i>)	32b
(9) ^a		 (2.0 equiv)	 (99%, 5:1)	32d

^a Catalyzed by 34. ^b Catalyzed by 32. ^c Regioisomeric ratio = 3:1.

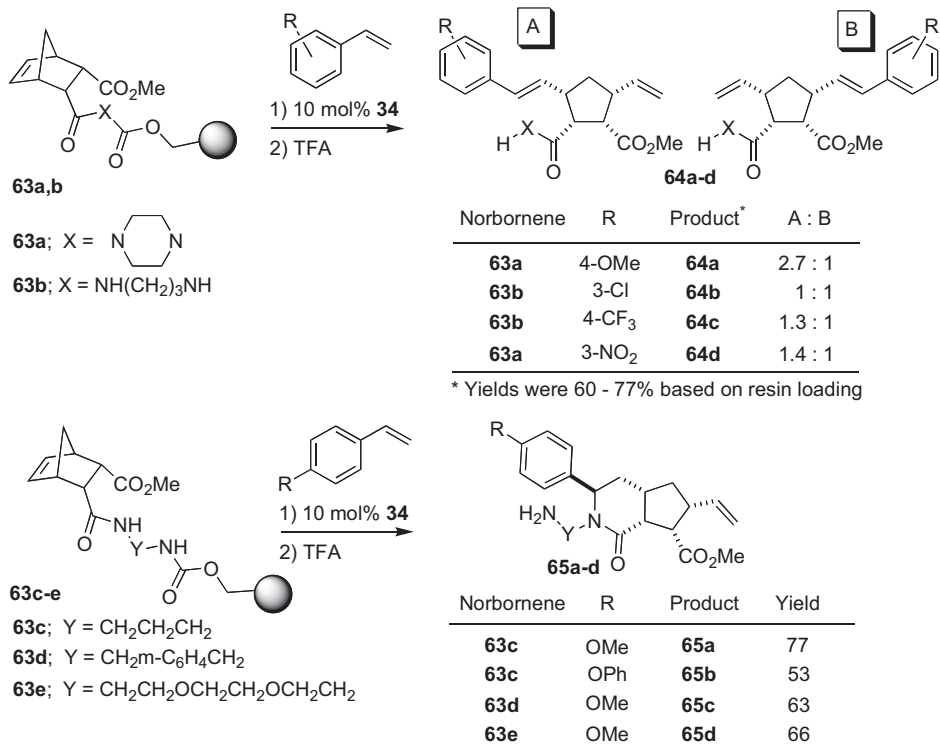
Tab. 2.6-6. ROCM reactions of oxabicyclo[3.2.1]octene derivatives with terminal olefins.

Entry	Cycloolefin (X, Y)	R	Catalyst	Product yield	Ref.
(1)	(O)	<i>p</i> -tBuPh	34	83%	35a
(2)	(O)	Ph	34	65%	35b
(3)	(O)	Ph	62	83%	35a
(4)	(O)	BrCH ₂	62	71%	35a
(5)	(OTBS, H)	Ph	62	60%	35a
(6)	(H, OTBS)	Ph	62	67%	35a

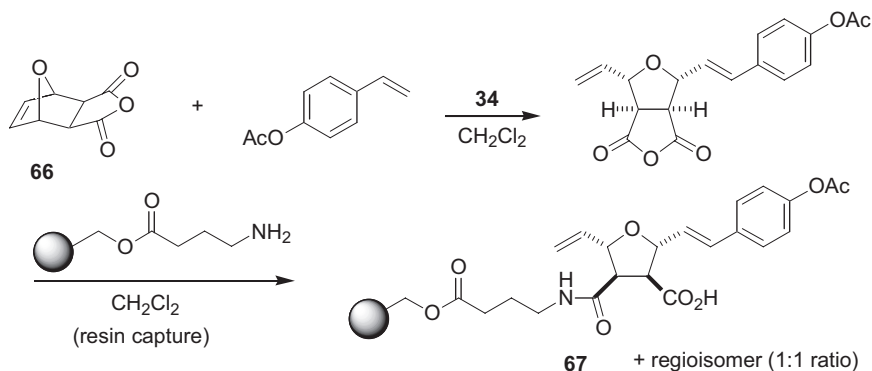


ROCM reactions of oxabicyclo[3.2.1]octane derivatives with terminal olefins have been utilized to prepare differentially substituted 4-pyrones as seen in Table 2.6-6 [35]. For entries 3–6, the more active *N*-heterocyclic carbene-containing catalyst **62** was employed [36]. In all cases the *E*-isomer was formed exclusively.

Cuny and coworkers have broadened the scope of the norbornyl ROCM to include solid-phase transformations [32a]. Attachment of an unsymmetrical norbornene derivative, using assorted diamine linkers (X), to Wang resin provided a series of bicyclic alkene substrates (**63a–d**) for ROCM (Scheme 2.6-13). Treatment of the resin-bound cycloolefins, **63a–b**, with a variety of substituted styrenes in the presence of 10 mol% **34**, followed by cleavage with TFA, gave ring-opened products (**64a–d**) in good yields. Interestingly, when substrates bearing primary diamine linkers (**63c–e**) were reacted with styrenyl ethers, the lactams **65a–d** were isolated after resin cleavage. Remarkably, in each case the reaction gave only one regioisomer.



Scheme 2.6-13. ROCM of norbornyl systems on solid support.



Scheme 2.6-14. Resin-capture of ROCM products.

As an alternative strategy to solid-phase ROCM, “resin-capture” of ROCM products, was also described (Scheme 2.6-14) [32b]. For example, the crude reaction mixture of the ROCM of **66** with 4-acetoxy styrene was combined with resin (Wang)-bound γ -amino butyric acid (GABA) to give compound **67** as a mixture of

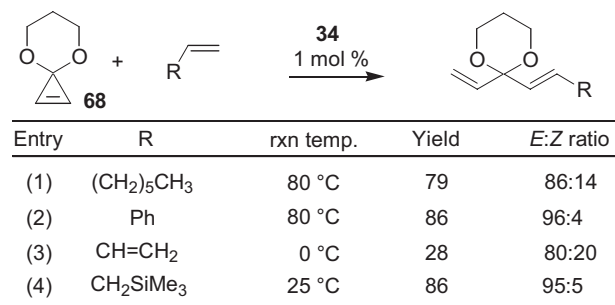
regioisomers (1:1 ratio). In this resin capture, the carboxylate functionality is unmasked. The introduction of this diversity element creates a means to initiate a combinatorial library synthesis, via ROCM, in solution. The solution-phase ROCM products are then transferred to the solid support for subsequent transformations.

2.6.3.4

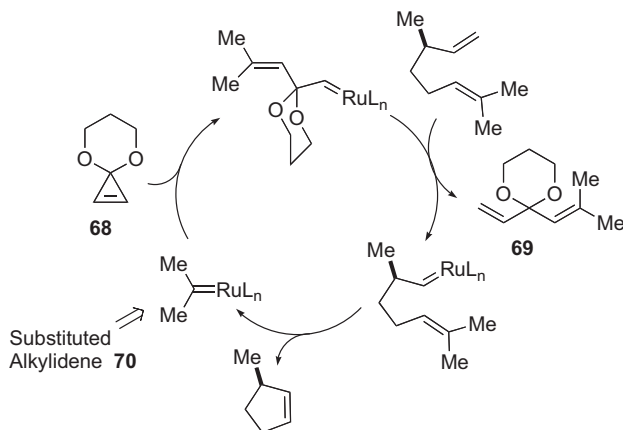
ROCM Reactions of Cyclopropenes

The selective ROCM of cyclopropene **68** with several monosubstituted olefins using catalyst **34** has also been described (Scheme 2.6-15) [37]. The protocol allows for the preparation of protected dialkenyl-substituted ketones. In all cases the *E*-isomer is formed predominately over the *Z*-isomer.

Insight into the nature of the active alkylidene species for the ROCM reactions of cyclopropene **68** was gained by examining the reaction products generated in the ROCM of **68** with citronellene (Scheme 2.6-16). The formation of ring-opened product **69** along with the ring-closed product (*R*)-2-methyl cyclopentene supports a substituted alkylidene complex (**70**) as the active species.



Scheme 2.6-15. ROCM of cyclopropenes.

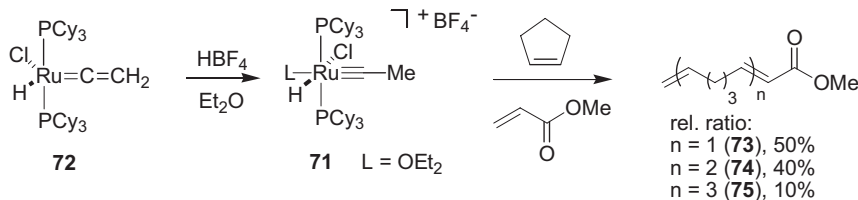


Scheme 2.6-16. Identification of the propagating alkylidenes in the rocm of cyclopropenes.

2.6.3.5

ROCM Reactions Involving Unstrained Cycloolefins

In 1998, Werner and coworkers reported the first successful ROCM involving a relatively unstrained cycloolefin [38] promoted by a “well-defined” catalytic system [39]. Carbynehydridoruthenium complex (**71**) generated *in situ* from the reaction of ruthenium complex **72** with hydrogen tetrafluoroborate catalyzed the ROCM of cyclopentene with methyl acrylate to give unsymmetrical products **73**, **74**, and **75** in a 5:4:1 ratio (Scheme 2.6-17).



Scheme 2.6-17. Cyclopentene ROCM.

More recently, the ROCM reactions of unstrained cycloalkenes with α,β -unsaturated carbonyl compounds using the more active N-heterocyclic carbene (NHC)-containing ruthenium catalysts **62** or **76** (Table 2.6-7) have been demonstrated independently by Grubbs and Blechert [40]. The products of these reactions are symmetrical molecules in which 2 equivalents of the terminal olefin are incorporated, indicating an ROCM/CM reaction sequence. In all cases only the *E*-isomer was observed. Typically, an excess of cyclic olefin is required to suppress dimerization of the electron-deficient terminal olefin. In Blechert's studies, it was reported that the phosphine-free catalyst **76** developed by Hoveyda and coworkers [41] was superior to catalyst **62** in these reactions (entry 1 vs. entry 2).

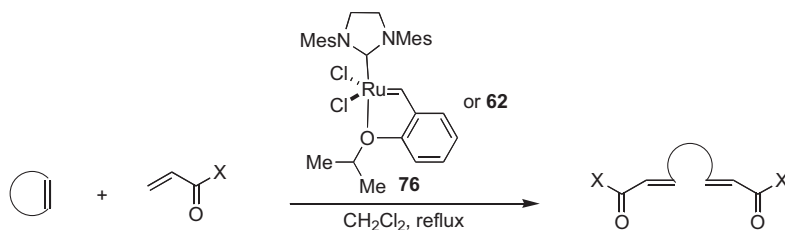
Mechanistic rationale for the observed products in the ROCM of unstrained olefins with α,β -unsaturated carbonyl compounds has been suggested (Scheme 2.6-18). The ring opening is believed to occur via the enoic carbene (**77**), a species that is relatively slow to form but highly reactive towards metathesis [42]. After reaction with the unstrained cycloolefin, the newly formed alkylidene **78** reacts preferentially with a second molecule of the terminal alkene-generating product **79**, and ruthenium methyldiene **80**, which will then react with the electron-deficient olefin to regenerate **77**.

2.6.3.6

ROCM Reactions of Trisubstituted Olefins

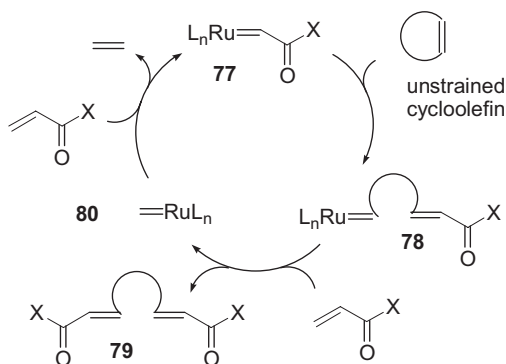
Recently, Grubbs et al. reported the ROCM of trisubstituted cycloolefins with unsaturated esters and ketones (Scheme 2.6-19) [43]. The products generated are unsymmetrical acyclic dienes. The newly formed α,β -unsaturated alkenes are all of the *E*-orientation. The low yields associated with the ring opening of the less

Tab. 2.6-7. ROCM reactions of unstrained cyclic olefins with α,β -unsaturated carbonyls.

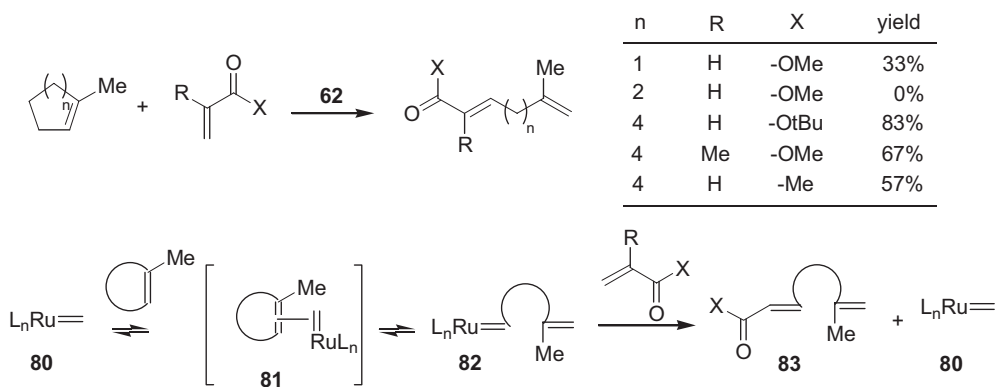
						
Entry	Catalyst ^a	Cycloolefin ^b	X	Product	(Yield)	Ref.
(1)	76		Me		(86%)	40a
(2)	62		Me		(62%)	40a
(3)	76		OH		(60%)	40a
(4)	76		OMe		(66%)	40a
(5)	62		OtBu		(88%)	40b
(6)	62		OH		(94%)	40b
(7)	76		OMe		(97%)	40a
(8)	76		Me		(75%)	40a
(9)	76		OH		(80%)	40a

^aCatalyst loading 5 mol%. ^b2–3 equivalents of cycloolefin.

strained olefins methylcyclohexene and methylcyclopentene suggest that the ring-opening species is the ruthenium methylidene **80**. The ruthenium methylidene **80** reacts in the orientation shown (**81**), placing the bulky ligands on the ruthenium away from the methyl group on the olefin. The new alkylidene **82** then reacts preferentially with the acrolal species to regenerate methylidene **80** and the unsymmetrical product **83**.



Scheme 2.6-18. ROCM between unsaturated alkenes and unstrained olefins.



Scheme 2.6-19. ROCM with trisubstituted cyclic olefins.

2.6.3.7

Variations of ROCM

A variant of ROCM, which should be addressed more thoroughly in the review of tandem metatheses, involves a sequential ROCM, followed by an intramolecular metathesis (i.e., RCM). In general, these processes are thermodynamically controlled by one of two manifolds. An enthalpy-driven ROCM/RCM may occur via the release of ring strain of the starting cycloolefin to form a more stable product. Alternatively, a ROCM/RCM may be entropically driven, through the release of a volatile byproduct, usually ethylene, even if the reaction product is enthalpically disfavored.

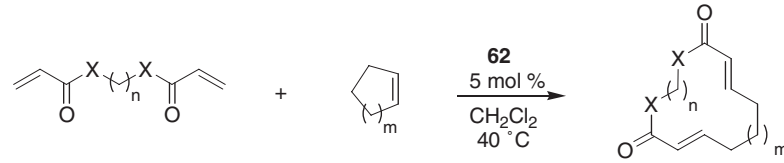
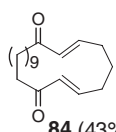
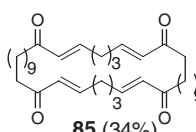
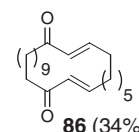
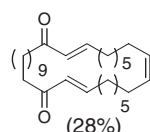
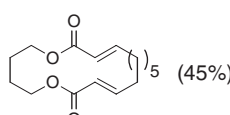
2.6.3.8

Ring Expansion via Olefin Metathesis

A variation of ROCM/RCM reaction involving the ring opening of a cyclic olefin with an acyclic diene can be used to yield ring-expanded products. Grubbs and

coworkers demonstrated this ring-expansion methodology towards the synthesis of macrocycles (Table 2.6-8) [44]. This reaction involves three types of olefin metathesis reactions (ROCM, CM, and RCM) occurring sequentially (Scheme 2.6-20). By varying the concentration (entry 1 vs. entry 2) of the reaction and the stoichiometry of the cycloalkenes (entry 3 vs. entry 4), a dramatic effect on the product distribution is possible.

Tab. 2.6-8. Ring-expansion metathesis reactions.

				
Entry	Diene (X, n)	Cycloolefin (m, equiv)	Conc. (mM)	Products ^a (yield)
(1)	(CH ₂ , 8)	(1, 5.0)	(5)	 84 (43%) +  85 (34%)
(2)	(CH ₂ , 8)	(1, 5.0)	(25)	84 (13%) + 85 (30%)
(3)	(CH ₂ , 8)	(4, 2.0)	(5)	 86 (34%) +  (28%)
(4)	(CH ₂ , 8)	(4, 1.1)	(5)	86 (53%)
(5)	(O, 4)	(4, 1.1)	(5)	 (45%)

^a All α,β -unsaturated carbonyl olefins are the *E*-isomers.



Scheme 2.6-20. Ring expansion initiated by a ROCM.

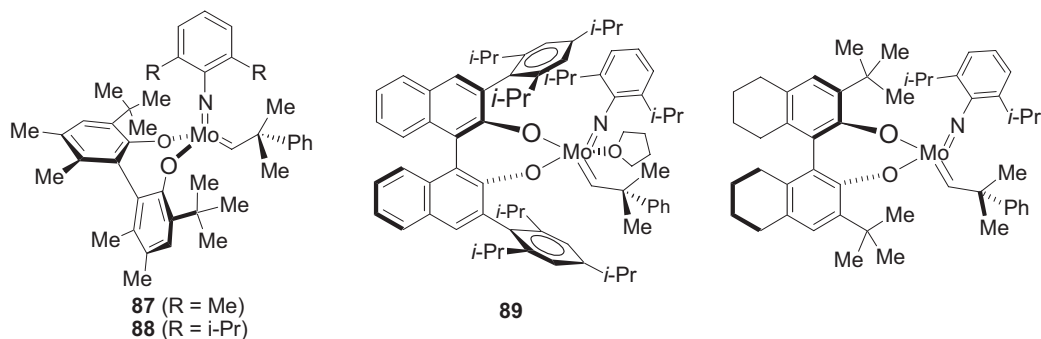


Fig. 2.6-2. Chiral molybdenum-based metathesis catalysts.

2.6.4

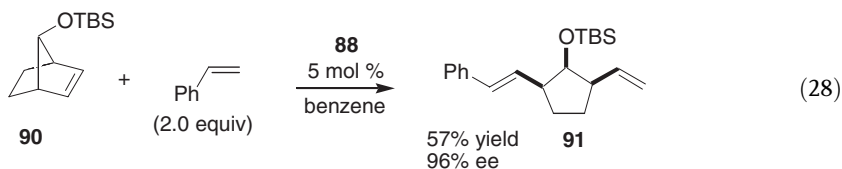
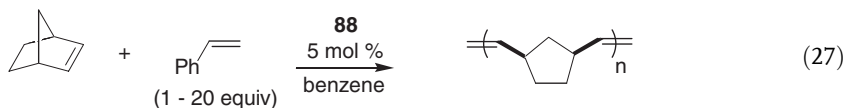
Enantioselective ROCM

Collaborative efforts between the Schrock and Hoveyda laboratories have led to the development of chiral molybdenum-based complexes (Figure 2.6-2), complexes that promote an efficient, catalytic asymmetric ring-closing metatheses (ARCM) [45]. The chiral biphen-based catalysts **87** and **88**, as well as the binaphtholate complex **89**, would also prove highly effective at catalyzing a number of asymmetric ring-opening cross-metatheses (AROCM) and tandem asymmetric ring-opening/ring-closing metatheses (AROCM/RCM). The topic of asymmetric ROCM will be covered in greater detail in the chapter on enantioselective olefin metatheses; however, a few AROCM will be included in this review.

2.6.4.1

Mo-Catalyzed Asymmetric ROCM

All examples of enantioselective ROCM to date have employed the use of norbornyl systems and terminal monosubstituted olefins as metathesis partners. An initial attempt to effect the ROCM of styrene with norbornene using catalyst **88** (5 mol%), resulted in the rapid formation of oligomeric products with <5% non-oligomeric adducts (Eq. (27)) [46]. It was later realized, however, that successful AROCM could be achieved using the more hindered 7-*t*-butyldimethylsiloxy-norbornene **90**, giving desired ring-opened product **91** as a single olefin isomer (*E*) in 57% isolated yield and 96% *ee* (Eq. (28)).



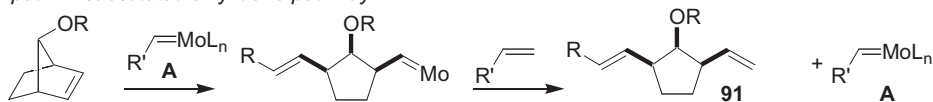
Tab. 2.6-9. AROCM of norbornenes with terminal olefins.

Entry	Norbornene	R	Product	% Yield	% EE
(1)		<i>p</i> -CF ₃ C ₆ H ₄		80	>98
(2)		<i>p</i> -OMeC ₆ H ₄		92	>98
(3)		Ph		94	>98
(4)		Ph		84	>98
(5)		Ph		98	98
(6)		Si(Me) ₃		62	>98

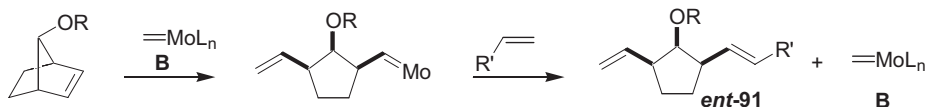
The AROCM of 7-*O*-substituted norbornyl systems with terminal olefins proved to be quite general (Table 2.6-9). A wide range of terminal alkenes could be used as reaction partners, including electron-rich aromatics (entry 2), electron-deficient aromatics (entry 1), and vinyl silanes (entry 6). More functionalized norbornyl systems could be used as well (entries 3, 4, and 5), providing a scaffold for further functionalization.

One of the most critical issues concerning the mechanism of the AROCM reaction is the identity of the various alkylidenes generated during the course of the reaction. In the catalytic enantioselective variant of the ROCM, it is particularly important that the reaction proceed exclusively through either the substituted Mo-alkylidene or the Mo-methylidene (Scheme 2.6-21). If AROCM occurs with the same enantiofacial selectivity in both cases, then path I and II would lead to opposite enantiomers, producing **91** and *ent*-**91**, respectively. Moreover, if both pathways were operative, reduced enantioselection would be observed. The high degree of

path I - substituted alkylidene pathway



path II - methyldiene pathway



Scheme 2.6-21. Alkylidenes in Mo-catalyzed AROCM.

enantioselectivity observed for the AROCM of norbornyl systems with terminal olefins suggests that a single pathway is responsible for product formation.

Several pieces of evidence suggest that the substituted alkylidene is the propagating alkylidene in the catalytic AROCM (i.e., path I, Scheme 2.6-21). The widely varying degrees and rates of reactivity between different terminal olefins can be rationalized better by stabilization and/or destabilization of their corresponding Mo alkylidenes. In addition, treatment of catalyst **88** with 40 equivalents of styrene in C_6D_6 leads to immediate generation of the Mo benzyldiene, indicating that formation of the Mo benzyldiene is highly rapid and favorable.

2.6.4.2

A Recyclable Chiral Ruthenium Catalyst for Asymmetric ROCM

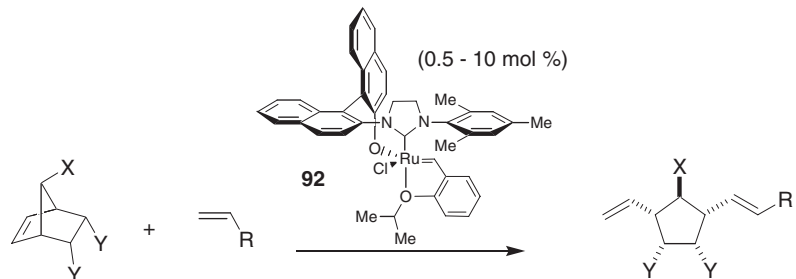
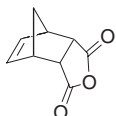
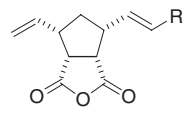
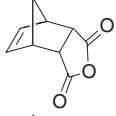
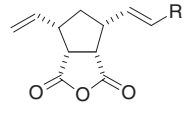
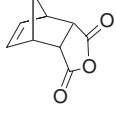
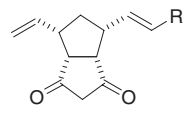
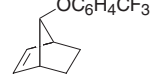
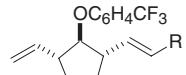
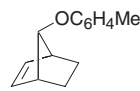
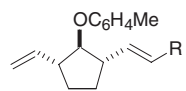
Hoveyda and coworkers recently described the preparation of a chiral ruthenium-based complex (**92**) for enantioselective olefin metathesis (Table 2.6-10) [47]. Complex **92** is air stable, can be purified by silica gel chromatography, and is able to be recovered in good yields from metathesis reactions. Catalyst **92** promotes the AROCM of norbornyl systems with various aromatic and aliphatic terminal olefins, giving dienes in good yields, high optical purities, and exclusive *E*-stereochemistry of the 1,2-disubstituted olefin in the products. Moreover, none of the transformations in Table 2.6-10 could be carried out with the previously mentioned chiral molybdenum-based catalysts.

2.6.5

ROCM in Total Synthesis

The emergence of the well-defined, substrate-tolerant ruthenium- and molybdenum-based complexes has opened the door for olefin metathesis as a validated synthetic method. The earliest examples of olefin metathesis in synthesis employed these catalysts for RCM, providing efficient access to ring systems that may have been difficult to synthesize by alternative methods [48]. As the scope and

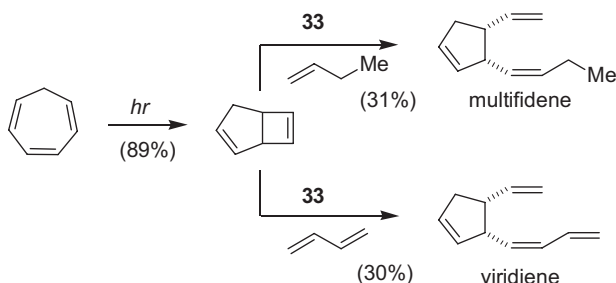
Tab. 2.6-10. AROCM reactions catalyzed by chiral complex **92**.

						
Entry	Norbornene	R	Product	% Yield	% EE	% Cat. recovery
1		Ph		71	80	96
2		n-C ₅ H ₁₁		57	80	92
3		Cy		60	82	88
4		Ph		66	96	86
5		Ph		76	95	71

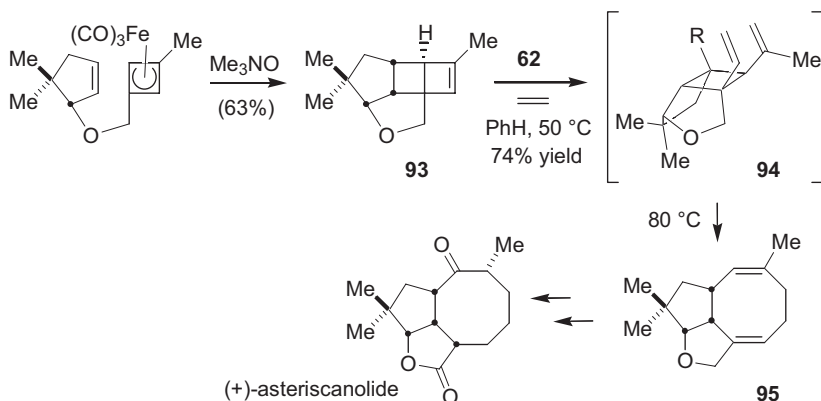
factors that effect ROCM processes have become better understood, ROCM has also begun to find service in target-oriented synthesis.

For example, the selective ROCM involving bicyclo[3.2.0]heptenes with terminal olefins allowed for the expedient synthesis of the brown algae pheromones multi-fidene and viridiene (Scheme 2.6-22) [27]. Starting from commercially available cycloheptatriene, these two-step total syntheses delivered each natural product in nearly 30% overall yield. These new routes represent a notable improvement over previously reported syntheses, all of which required approximately 9–11 steps to produce these brown algae pheromones in low single-digit overall yields [49].

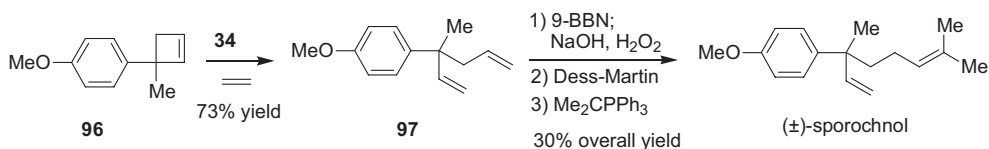
Asteriscanolide has been also prepared through several synthetic strategies, offering the natural product in approximately 13–18 steps, depending on the



Scheme 2.6-22. Total synthesis of multifidene and viridene.



Scheme 2.6-23. A ROCM/cope rearrangement in the total synthesis of asteriscanolide.



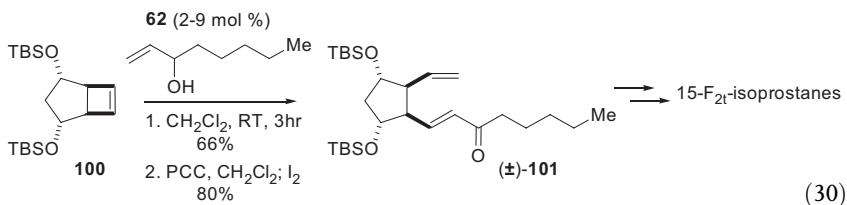
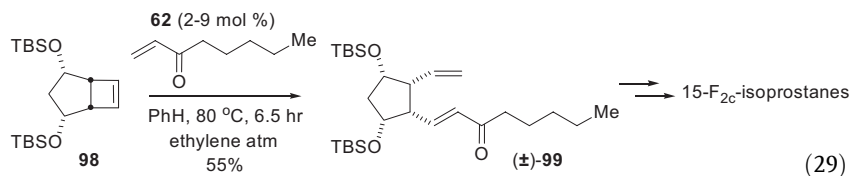
Scheme 2.6-24. ROCM in the synthesis of sporochinol.

route [50]. In comparison, Scheme 2.6-23 illustrates a sequential ROCM/Cope rearrangement strategy for the preparation of (+)- and (−)-asteriscanolide [51]. The ROCM of a strained trisubstituted olefin (compound **93**) with ethylene provides divinylcyclobutane intermediate **94**, which undergoes a Cope rearrangement at 80 °C to give **95** in 74% overall yield. The tandem ROCM, Cope rearrangement was carried out in one pot simply by heating the reaction from 50 °C to 80 °C after the ROCM was complete. Two additional steps were used to complete the synthesis of natural product, providing asteriscanolide in a total of nine steps for the longest linear sequence.

In a related fashion, the ROCM of cyclobutene **96** with ethylene to give **97** was reported recently by Harrity et al. [52] (Scheme 2.6-24). Selective hydroboration of the less sterically hindered alkene, followed by oxidation and Wittig olefination, gave (±)-sporochinol in 30% yield from **97**.

Likewise, the 15-F₂-isoprostane family was also prepared using ROCM as a key transformation. The isoprostanes represent an intriguing class of lipid metabolites whose function is unclear at present [53]. While structurally related to the well-known prostaglandins, the *cis*-relationship of the isoprostane aliphatic side chains on the cyclopentane ring introduce significant differences to both the metabolites' cellular activities, as well as to their possible laboratory syntheses. Furthermore, since the biological preparation of the isoprostanes may not be stereospecific, a route toward all the possible isoprostanes would be advantageous. Figure 2.6-3 illustrates the family of 15-F₂-isoprostanes.

The use of ROCM as a key transformation for the preparation of the 15-F₂-isoprostanes and analogues is illustrated in Eqs. (29) and (30) [54]. For the *cis*-series, ROCM with pentyl vinyl ketone provides the desired ring-opened product as a racemic mixture (Eq. (29)). Alternatively for the *trans*-series, ROCM with 1-octen-3-ol, followed by oxidation and olefin isomerization, generates the desired racemic ROCM product as a single olefin isomer (Eq. (30)). With the stereochemistry of the side chains established through the ROCM, the side chains were then elaborated into the isoprostane functionality.



Completion of the isoprostanes required independent functionalization of the *cis*-side chains introduced in the ROCM step. Overall, the ROCM step allows for the preparation of all of the 15-F₂-isoprostanes in an efficient 10–12 steps, depending on the particular isomer. The availability of all the isoprostanes, both known and anticipated, should allow for a better understanding of the biological role of these novel lipid metabolites.

2.6.6

Conclusions

The wide variety of transformations that olefin metatheses encompass, along with the advent of user-friendly, substrate-tolerant, and commercially available metathesis catalysts, have broadened the range of technologies available for organic

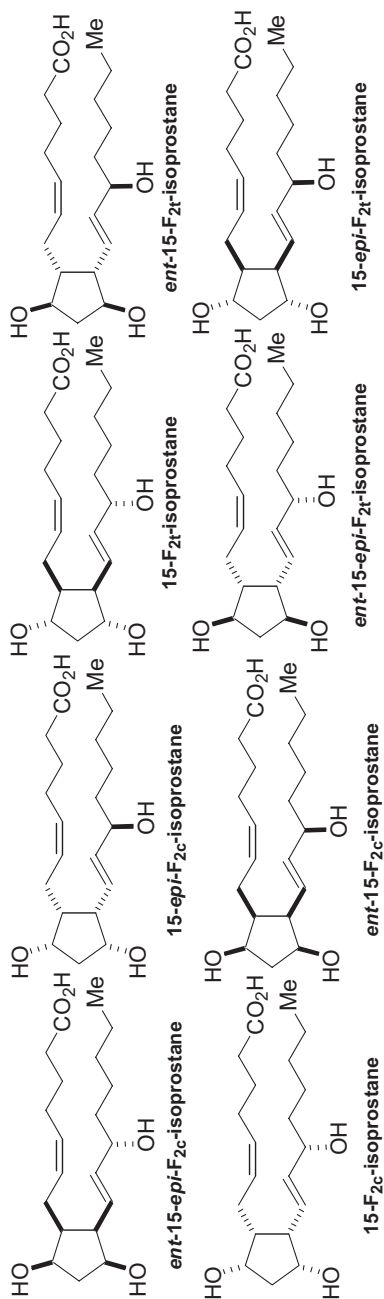


Fig. 2.6-3. The 15-F₂-isoprostanes.

synthesis. In this regard, it has become clear that ROCM has emerged as a reliable, unique, and useful synthetic methodology. Efforts to understand the complexities and factors that govern the critical selectivity issues in this cross-metathesis have uncovered a reaction that is highly tunable, allowing for subtle adjustments in reaction parameters to produce desired effects. The ability to perform selective and highly efficient ROCM processes has further increased the scope of olefin metathesis processes, providing a suitable complement to RCM, CM, ROMP, and ADMET chemistry.

References

- For reviews on RCM, see: (a) MAIER, M. E. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077. (b) ARMSTRONG, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (c) FÜRSTNER, A. *Topics in Catalysis* **1997**, *4*, 285–299. For selected books and reviews on ROMP chemistry, see: (d) DRAGUTAN, V.; STRECK, R. *Catalytic Polymerization of Cycloolefins: Ionic, Ziegler-Natta and Ring-Opening Metathesis Polymerization. Studies in Surface Science and Catalysis*; Elsevier: Amsterdam. 2000; Vol. 131. (e) BUCHMEISER, M. R. *Chem. Rev.* **2000**, *100*, 1565–1604. (f) NOELS, A. F. J. *Phys. Org. Chem.* **1998**, *11*, 602–609. Also, see: (g) IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997. (h) RANDALL, M. L.; SNAPPER, M. L. *J. Mol. Catal. A* **1998**, *133*, 29–40.
- For selected examples of CM involving acyclic alkenes, see: (a) CHATTERJEE, A. K.; MORGAN, J. P.; SCHOLL, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784. (b) AHMED, M.; ARNAULD, T.; BARRETT, A. G. M.; BRADDOCK, D. C.; FLACK, K.; PROCOPIOU, P. A. *Org. Lett.* **2000**, *2*, 551–553. (c) RANDL, S.; GESSLER, S.; WAKAMATSU, H.; BLECHERT, S. *Synlett* **2001**, *8*, 430–432. (d) CROWE, W. E.; GOLDBERG, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162–5163.
- TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
- (a) SCOTT, K. W.; CALDERON, N.; OFSTEAD, E. A.; JUDY, W. A. *Advances in Chemistry Series*; GOULD, R. F., Ed.; American Chemical Society: Washington, D.C., 1969; Vol. 91, Chapter 26, pp 399–418. (b) REIF, L.; HÖCKER, H. *Macromol. Chem. Rapid Commun.* **1981**, *2*, 183–185.
- BRADSHAW, C. P. C.; HOWMANN, E. J.; TURNER, L. J. *Catal.* **1967**, *7*, 269–276.
- This is based on the assumption that the rate determining step for the pairwise mechanism involves the formation of the metal-stabilized cyclobutane intermediate shown in Figure 2.6-1, and that displacement of olefins from this complex (a.k.a. “sticky olefin hypothesis”; see JOHN A. TALLARICO, Ph.D. Dissertation, Boston College, 1999; Chapter 3) to form a new metal-stabilized cyclobutane would be relatively slow.
- (a) HERRISON, J.-L.; CHAUVIN, Y. *Makromol. Chem.* **1970**, *141*, 161–176. (b) SOUFFLET, J.-P.; COMMEREUC, D.; CHAUVIN, Y. *Acad. Sci. Ser. C. (Hebd. Seances Acad. Sci. Ser. C.)* **1973**, *276*, 169–171. (c) CHAUVIN, Y.; COMMEREUC, D.; ZABROWSKI, G. *Makromol. Chem.* **1978**, *179*, 1285–1290.
- It can be postulated that dienes **1** and **3** could be accounted for by the “pairwise” mechanism in secondary processes.
- For an early review on mechanistic aspects of olefin metathesis, including other early examples of ROCM, see: CALDERON, N.; OFSTEAD, E. A.; JUDY, J. A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 401–409.
- KATZ, T. J.; MCGINNIS, J. J. *Am. Chem. Soc.* **1975**, *97*, 1592–1594.
- If the displacement reaction were rate-determining (see ref. 6), the data

could be explained by the conventional pair-wise mechanism.

- 12 ZUECH, E. A.; HUGHES, W. B.; KUBICEK, D. H.; KITTLEMAN, E. T. *J. Am. Chem. Soc.* **1970**, *92*, 528–531.
- 13 PINAZZI, C. P.; GUILMET, M. I.; REYX, D. *Tetrahedron Lett.* **1976**, 989–992.
- 14 ROSSI, R.; DIVERSI, P.; LUCHERINI, A.; PORRI, L. *Tetrahedron Lett.* **1974**, 879–882.
- 15 WILSON, S. R.; SCHALK, D. E.; *J. Org. Chem.* **1976**, *41*, 3928–3930.
- 16 (a) NOELS, A. F.; DEMONCEAU, A.; CARLIER, E.; HUBERT, A. J.; MÁRQUEZ-SILVA, R.-L.; SÁNCHEZ-DELGADO, R. A. *J. Chem. Soc., Chem. Commun.* **1988**, 783–784. For other early examples of ROMP and ROCM reactions giving asymmetrical products, see: (b) KATZ, T. J.; MCGINNIS, J.; ALTUS, C. *J. Am. Chem. Soc.* **1976**, *98*, 606–608. (c) BENCZE, L.; IVIN, K. J.; ROONEY, J. J. *J. Chem. Soc. Chem. Commun.* **1980**, 834–835. Also see ref. 9.
- 17 TEBBE, F. N.; PARSHALL, G. W.; REDDY, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.
- 18 HOWARD, T. R.; LEE, J. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6878–6880.
- 19 STRAUS, D. A.; GRUBBS, R. H. *J. Mol. Catal.* **1985**, *28*, 9–25.
- 20 STILLE, J. R.; SANTARSIERO, B. D.; GRUBBS, R. H. *J. Org. Chem.* **1990**, *55*, 843–862.
- 21 STILLE, J. R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855–856.
- 22 COUTURIER, J.-L.; TANAKA, K.; LECONTE, M.; BASSET, J.-M.; OLLIVER, J. *Angew. Chem. Int. Ed.* **1993**, *32*, 112–113.
- 23 BESPALOVA, N. B.; BOVINA, M. A.; SERGEEVA, M. B.; OPPENGEIM, V. D.; ZAIKIN, V. G. *J. Mol. Catal.* **1994**, *90*, 21–27.
- 24 SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DIMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.
- 25 Although the Grubbs' group has prepared several ruthenium-based complexes that catalyze metathesis reactions, the ruthenium-benzylidene catalyst **34** is commonly referred to as "Grubbs' catalyst." Subsequently, a more active version of this catalyst (**62**) was introduced (see Table 2.6-6) designating catalyst **34** as a "first-generation Grubbs' catalyst."
- 26 (a) NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859. (b) SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Int. Ed. Engl.* **1995**, *34*, 2039–2041.
- 27 RANDALL, M. L.; TALLARICO, J. A.; SNAPPER, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610–9611.
- 28 SNAPPER, M. L.; TALLARICO, J. A.; RANDALL, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478–1479.
- 29 (a) TALLARICO, J. A.; BONITATEBUS, JR. P. J.; SNAPPER, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157–7158. (b) TALLARICO, J. A.; RANDALL, M. L.; SNAPPER, M. L. *Tetrahedron* **1997**, *53*, 16511–16520.
- 30 SCHNEIDER, M. F.; LUCAS, N.; VELDER, J.; BLECHERT, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 257–259.
- 31 SCHNEIDER, M. F.; BLECHERT, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 411–412.
- 32 (a) CUNY, G. D.; CAO, J.; HAUSKE, J. R. *Tetrahedron Lett.* **1997**, *38*, 5237–5240. (b) CUNY, G. D.; CAO, J.; SIDHU, A.; HAUSKE, J. R. *Tetrahedron* **1999**, *55*, 8169–8178. (c) KARLOU-EYRISCH, K.; MÜLLER, B. K. M.; HERZIG, C.; NUYKEN, O. *J. Organomet. Chem.* **2000**, *606*, 3–7. (d) KATAYAMA, H.; URUSHIMA, H.; NISHIOKA, T.; WADA, C.; NAGAO, M.; OZAWA, F. *Angew. Chem. Int. Engl.* **2000**, *39*, 4513–4515. (e) ISHIKURA, M.; SAIJO, M.; HINO, A. *Heterocycles* **2002**, *57*, 241–244. Also, see refs. 29b and 30.
- 33 ARJONA, O.; CSÁKÝ, A. G.; CARMEN MURCIA, M.; PLUMET, J. *J. Org. Chem.* **1999**, *64*, 9739–9741.
- 34 ARJONA, O.; CSÁKÝ, A. G.; CARMEN MURCIA, M.; PLUMET, J.; BELÉN MULA, M. *J. Organomet. Chem.* **2001**, *627*, 105–108.
- 35 (a) WRIGHT, D. L.; USHER, L. J.; ESTRELLA-JIMINEZ, M. *Org. Lett.* **2001**, *3*, 4275–4277. (b) RANDALL, M. L. Ph.D. Dissertation, Boston College, 1998; Chap. 3, pg 42.
- 36 SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953–956. Catalyst **62** is commonly referred

- to as "second-generation Grubbs' catalyst."
- 37 MICHAUT, M.; PARRAIN, J.-L.; SANTELLI, M. *Chem. Commun.* **1998**, 2567–2568.
 - 38 For purposes of this review, an unstrained cyclic alkene will be designated as a cycloalkene with an inherent ring strain of <10 kcal/mol (see Table 2.6-1).
 - 39 STUER, W.; WOLF, J.; WERNER, H.; SCHWAB, P.; SCHULZ, M. *Angew. Chem. Int. Ed.* **1998**, 37, 3421–3423. For the ROCM of unstrained cycloalkenes catalyzed by a WCl_6 /DSCB cocatalyst system (*vide supra*) see ref. 23.
 - 40 (a) RANDL, S.; CONNON, S. J.; BLECHERT, S. *Chem. Commun.* **2001**, 1796–1797. (b) CHOI, T.-L.; LEE, C. W.; CHATTERJEE, A. K.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, 123, 10417–10418.
 - 41 GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, 122, 8168–8179.
 - 42 ULMAN, M.; BELDERRAIN, T. R.; GRUBBS, R. H. *Tetrahedron Lett.* **2000**, 41, 4689–4693.
 - 43 MORGAN, J. P.; MORRILL, C.; GRUBBS, R. H. *Org. Lett.* **2002**, 4, 67–70.
 - 44 LEE, C. W.; CHOI, T.-L.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2002**, 124, 3224–3225.
 - 45 (a) ALEXANDER, J. B.; LA, D. S.; CEFALO, D. R.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1998**, 120, 4041–4042. (b) LA, D. S.; ALEXANDER, J. B.; CEFALO, D. R.; GRAF, D. D.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1998**, 120, 9720–9721. (c) ZHU, S.; CEFALO, D. R.; LA, D. S.; JAMIESON, J. Y.; DAVIS, W. M.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1999**, 121, 8251–8259. (d) AEILTS, S. L.; CEFALO, D. R.; BONITATIBUS, JR.; P. J.; HOUSER, J. H.; HOVEYDA, A. H.; SCHROCK, R. R. *Angew. Chem. Int. Ed.* **2001**, 40, 1452–1456.
 - 46 (a) LA, D. S.; FORD, J. G.; SATTELY, E. S.; BONITATEBUS, P. J.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, 121, 11603–11604. (b) LA, D. S.; SATTELY, E. S.; FORD, J. G.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2001**, 123, 7767–7778.
 - 47 VAN VELDHIJZEN, J. J.; GARBER, S. B.; KINGSBURY, J. S.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2002**, 124, 4954–4955.
 - 48 For lead references concerning the use of RCM reactions in organic synthesis see: (a) WRIGHT, D. L. *Curr. Org. Chem.* **1999**, 32, 75–79. (b) ARMSTRONG, S. K. *J. Chem. Soc. Perkins Trans. 1* **1998**, 371–388. See also refs. 1a & 1b.
 - 49 (a) BOLAND, W.; JAENICKE, L. J. *Org. Chem.* **1979**, 44, 4819–4824. (b) BOLAND, W.; NIEDERMAYER, U.; JAENICKE, L.; GOERISCH, H. *Helv. Chim. Acta* **1985**, 68, 2062–2073. (c) BURKS, J. E., JR.; CRANDALL, J. K. *J. Org. Chem.* **1984**, 49, 4663–4670. (d) PAQUETTE, L. A.; COGHIAN, M. J.; HAYES, P. C. *J. Org. Chem.* **1984**, 49, 4516–4518. (e) KRAMP, P.; HELMCHEN, G.; HOLMES, A. B. *J. Chem. Soc., Chem. Commun.* **1993**, 551–552.
 - 50 (a) CHEUNG, Y. Y.; KRAFFT, M. E.; JULIANO-CAPUCAO, C. A. *ACS 216th National Meeting Abstract*, **1998**, ORGN-238. (b) PAQUETTE, L. A.; TAE, J.; ARRINGTON, M. P.; SADOUN, A. H. *J. Am. Chem. Soc.* **2000**, 122, 2742–2748. (c) KRAFFT, M. E.; JULIANO-CAPUCAO, C. A. *Synthesis* **2000**, 1020. (d) WENDER, P. A.; IHLE, N. C.; CORREIA, C. R. D. *J. Am. Chem. Soc.* **1988**, 110, 5904–5906.
 - 51 LIMANTO, J.; SNAPPER, M. L. *J. Am. Chem. Soc.* **2000**, 122, 8071–8072.
 - 52 BASSINDALE, M. J.; HAMLEY, P.; HARRITY, J. P. A. *Tetrahedron Lett.* **2001**, 42, 9055–9057.
 - 53 (a) MORROW, J. D.; HILL, K. E.; BURK, R. F.; NAMMOUR, T. M.; BADR, K. F.; ROBERTS, L. J. II *Proc. Natl. Acad. Sci. USA* **1990**, 87, 9383–9387. (b) MORROW, J. D.; ROBERTS, L. J. II *Free Radical Biol. Med.* **1991**, 10, 195–200. (c) MORROW, J. D.; AWAD, J. A.; KATO, T.; TAKAHASHI, K.; BADR, K. F.; ROBERTS, L. J. II; BURK, R. F. *J. Clin. Invest.* **1992**, 90, 2502–2507. (d) MORROW, J. D.; AWAD, J. A.; BOSS, H. J.; BLAIR, I. A.; ROBERTS, L. J. II *Procl. Natl. Acad. Sci. USA* **1992**, 89, 10721–10725.
 - 54 (a) SCHRADER, T. O.; SNAPPER, M. L. *Tetrahedron Lett.* **2000**, 41, 9685–9688. (b) SCHRADER, T. O.; SNAPPER, M. L. *J. Am. Chem. Soc.* **2002**, 124, 10998–11000.

2.7

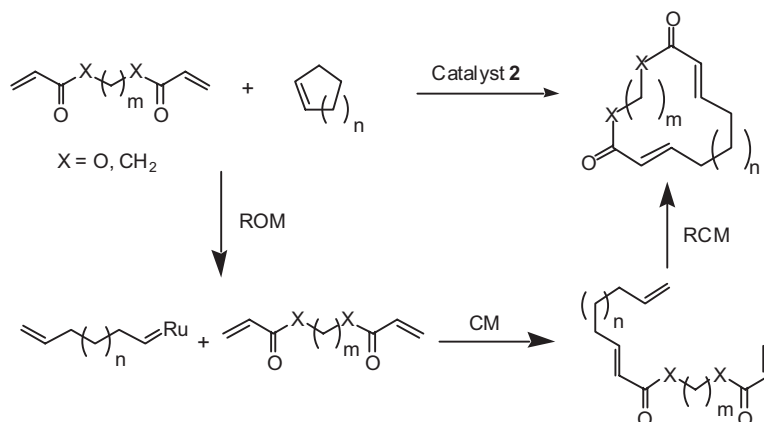
Ring-Expansion Metathesis Reactions

Choon Woo Lee

Formation of macrocycles has been a challenging problem in organic synthesis. Since olefin metathesis has provided a new approach to macrocyclization, the efficiency of this process has been improved by the emergence of ruthenium catalysts **1**, $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$, and **2**, $\text{Cl}_2(\text{PCy}_3)(\text{H}_2\text{IMes})\text{Ru}=\text{CHPh}$, due to their high activity, stability, functional group tolerance, and stability to air and moisture [1, 2]. Recently, Grubbs' group demonstrated a novel method of formation of macrocycles by ring-expansion metathesis reactions using catalyst **2** in which three types of olefin metathesis (ring-opening metathesis [ROM], cross-metathesis [CM], and ring-closing metathesis [RCM]) reactions occur sequentially to yield macrocycles (Scheme 2.7-1) [3].

Readily available cycloalkenes were expanded to provide a variety of macrocycles such as macrolactone and macrocarbocycle, depending on the acyclic diene linker. The concept of ring-expansion reaction, using olefin metathesis, is fundamentally different from the tandem ring-opening–ring-closing metathesis sequence (ROM-RCM). While ROM-RCM is also known as a “ring-rearrangement” or “ring-shuffling” reaction that proceeds in intramolecular fashion by tandem metathesis [4, 5], the ring-expansion metathesis reaction contains intermolecular ring expansion between a cycloalkene and a linker (acyclic diene), the type of which has not yet been established in the common chemical reaction (Scheme 2.7-2) [6].

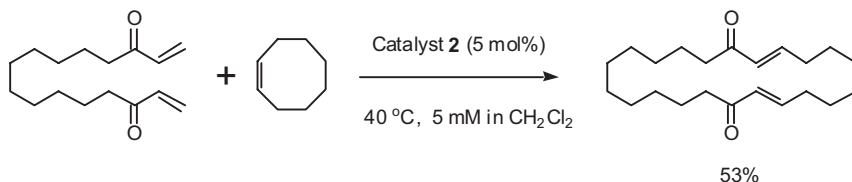
This ring-expansion metathesis methodology provides an efficient and mild technique for the synthesis of macrocycles – especially carbocycles – which is considered harder than macrolactonization or lactamization. For a successful ring-expansion metathesis, several conditions must be satisfied. First, the cycloalkenes must be able to undergo the ring-opening metathesis reaction. Second, once opened, it must react selectively with the acyclic diene for CM and RCM to minimize side products. Finally, the acyclic diene should not react with itself, e.g., cyclization or cross-metathesis, to form a dimer or oligomer. α,β -Unsaturated carbonyl compounds react less favorably with themselves and are known to react selectively with terminal olefins by metathesis using catalyst **2** in excellent yields [7]. For these reasons, diacrylates and divinyl ketones which are known to undergo selective cross metathesis were chosen as the acyclic dienes (e.g., linkers). For ex-



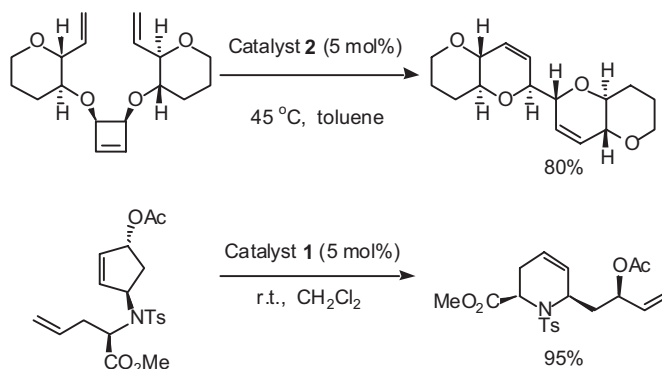
Catalyst 2: Cl₂(PCy₃)(H₂IMes)Ru=CHPh

Scheme 2.7-1. Ring-expansion metathesis reaction.

- Ring-expansion Metathesis Reaction

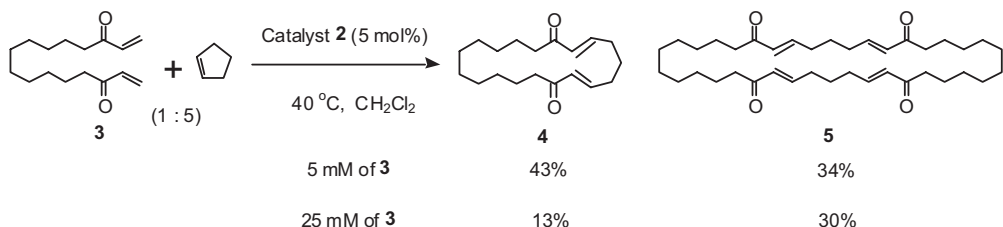


- Ring-rearrangement Metathesis Reaction

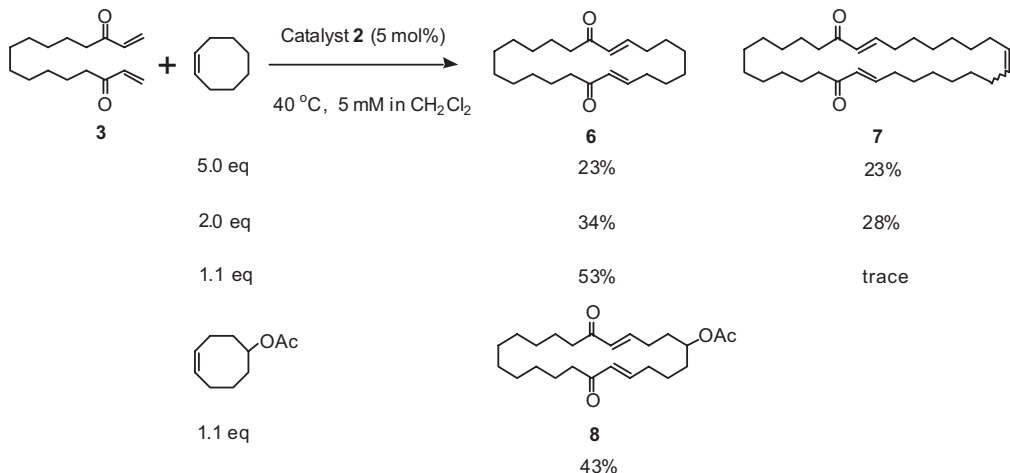


Scheme 2.7-2. Ring-expansion and ring-rearrangement metathesis reaction.

ample, cyclopentene and cyclooctene, which were known to perform ring-opening cross-metathesis (ROCM) using catalyst 2 with α,β -unsaturated carbonyl compounds [8, 9], were explored for the ring-expansion metathesis reaction with divinyl ketone 3 (Schemes 2.7-3 and 2.7-4). As shown in Scheme 2.7-3, when catalyst



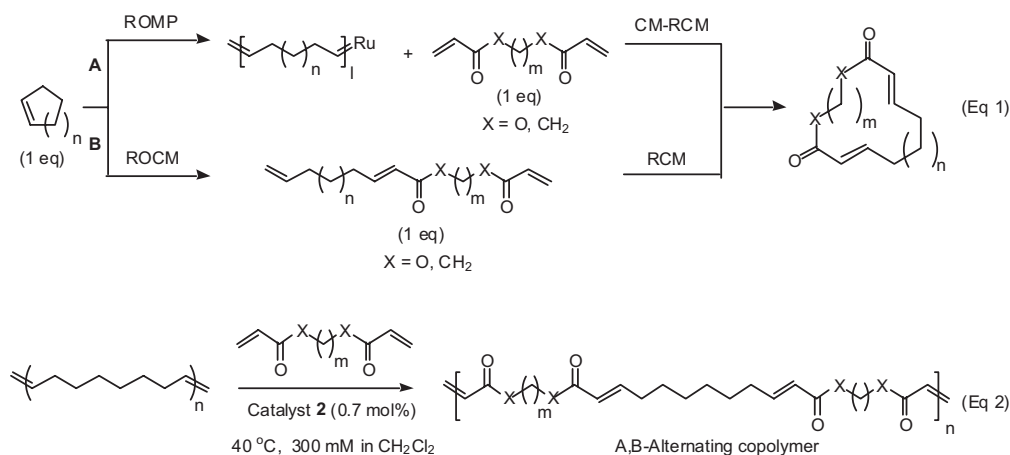
Scheme 2.7-3. Ring-expansion metathesis reaction of cyclopentene (less-strained olefin).



Scheme 2.7-4. Ring-expansion metathesis reaction of cyclooctene (high-strained olefin).

2 was added to a solution of **3** and cyclopentene in CH₂Cl₂, major products were the (1 + 1) fashion (**3** and cyclopentene) ring-expanded product **4** and the double-ring-expanded product **5**. Varying the concentration of **3** in the reaction changed the product ratio. As anticipated, increasing the concentration of **3** (5 mM to 25 mM) resulted in a decrease in the product ratio of **4**:**5** (1.3:1 to 1:2.3) [10]. At higher concentration, the yields of **4** and **5** also decreased due to the formation of the triple-ring-expanded product (9%) as well as competing higher oligomers.

Cyclopentene can be used in excess (5 equivalents) because the ROMP reaction of cyclopentene at high temperatures is less favorable, resulting in sequences of ROCM-RCM to afford the (1 + 1) fashion products. However, since cyclooctene with a higher ring strain undergoes ROMP much faster than cyclopentene [11], the relationship of cyclooctene's stoichiometry was expected to change the product distribution (Scheme 2.7-4). With 5 equivalents of cyclooctene, the desired (1 + 1) product **6** (23% yield) and the cyclooctene double-inserted product **7** were obtained as the major products while the remainder was higher oligomers. Decreasing the equivalence of cyclooctene to 2 increased the ratio to 1.2:1, and the best yield of 53% for the desired product **6** was isolated with 1.1 equivalents of cyclooctene.



Scheme 2.7-5. Pathways to the ring-expansion metathesis reaction.

Therefore, it is crucial to adjust the stoichiometry of cyclooctene as well as the reaction concentration carefully in order to control the distribution of macrocycles. With the appropriate conditions, the ring-expansion metathesis reaction was extended to functionalized cyclic olefins. For instance, functionalized cyclooctene is also a viable substrate for ring expansion.

In the ring-expansion metathesis reaction, it is believed that two reaction sequences **A** and **B** compete as main pathways, depending on ring strain as well as reaction concentration (Eq. (1) in Scheme 2.7-5). It is likely that cyclooctene prefers the pathway **A**, whereas for cyclopentene, pathway **B** dominates.

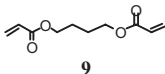
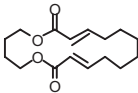
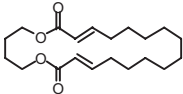
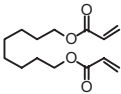
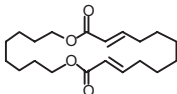
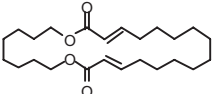
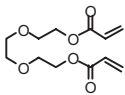
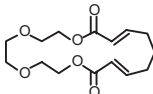
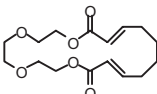
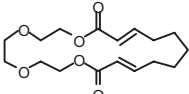
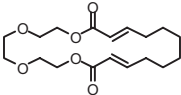
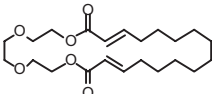

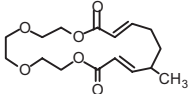
The treatment of the isolated cyclooctene ROMP product with α,β -unsaturated carbonyl compounds at high concentrations using catalyst **2** afforded the A,B-alternating copolymer in good yield (Eq. (2) in Scheme 2.7-5) [12]. Therefore, even if cyclooctene performs ROMP much faster than CM with acyclic diene, catalyst **2** exhibits sufficient activity to react with internal olefins of the polymer to yield the corresponding macrocycle.

Diacrylates are also useful linker units for ring expansion (Table 2.7-1) [3]. Substrates **9** and **12** gave 18- to 26-membered macrocycles with moderate yields (entries 1–4).


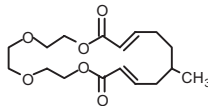
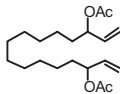
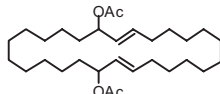
The best yields for ring expansion with cycloalkenes were obtained when diacrylate **15** was used (entries 5–9). Even though substrate **12** and **15** have the same number of linker units, the presence of fewer conformationally constraining oxygen atoms in **15** favors the formation of the desired monomeric products [10, 13, 14].

With the best substrates identified, various cycloalkenes were screened to create a library of macrocycles (entries 5–11). For cycloheptene, 5 equivalents were used, since the rates of the ring opening were slower than for cyclooctene. Higher concentrations of cyclopentene and cycloheptene resulted in significant side reactions and did not increase the yields of the desired product. The reaction with

Tab. 2.7-1. The extended scope of ring expansion^a [3].

Ent	Sub.	Ring size ^b (Eq.)	Ring products ^c	Yield ^d (%)
1	 9	8 (1.1)		10 (45)
2	9	12 (1.1)		11 (54)
3	 12	8 (1.1)		13 (47)
4	12	12 (1.1)		14 (42)
5	 15	5 (5.0)		16 (52)
6	15	6 (5.0)		17 (39)
7	15	7 (5.0)		18 (63)
8	15	8 (1.1)		19 (59)
9	15	12 (1.1)		20 (55)
10	15	 (5.0)		21 (50)

Tab. 2.7-1. (continued)

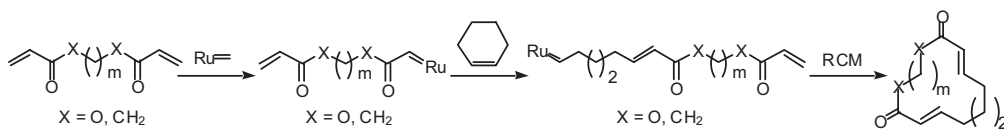
Ent	Sub.	Ring size ^b (Eq.)	Ring products ^c	Yield ^d (%)
11	15	 (5.0)		22 (37)
12	 23	12 (1.1)		24 (59)

^a Reactions were performed using catalyst **2** (5 mol%) in refluxing CH₂Cl₂ (5~8 mM) under an atmosphere of argon.

^b Ring size of cycloalkenes: 5, cyclopentene; 6, cyclohexene; 7, cycloheptene; 8, cyclooctene; 12, cyclododecene.

^c Only (*E*)-acrylates were observed by ¹H NMR.

^d Isolated yields. No starting linkers remained except in entries 6 and 11.

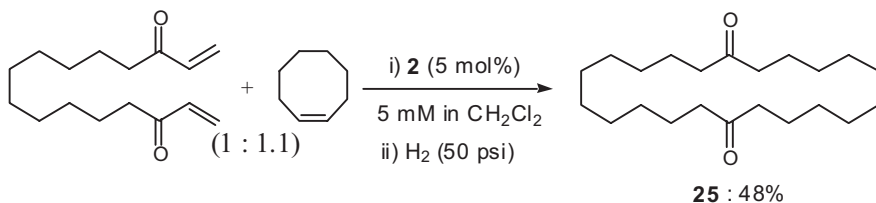


Scheme 2.7-6. Ring-expansion metathesis reaction (cyclohexene).

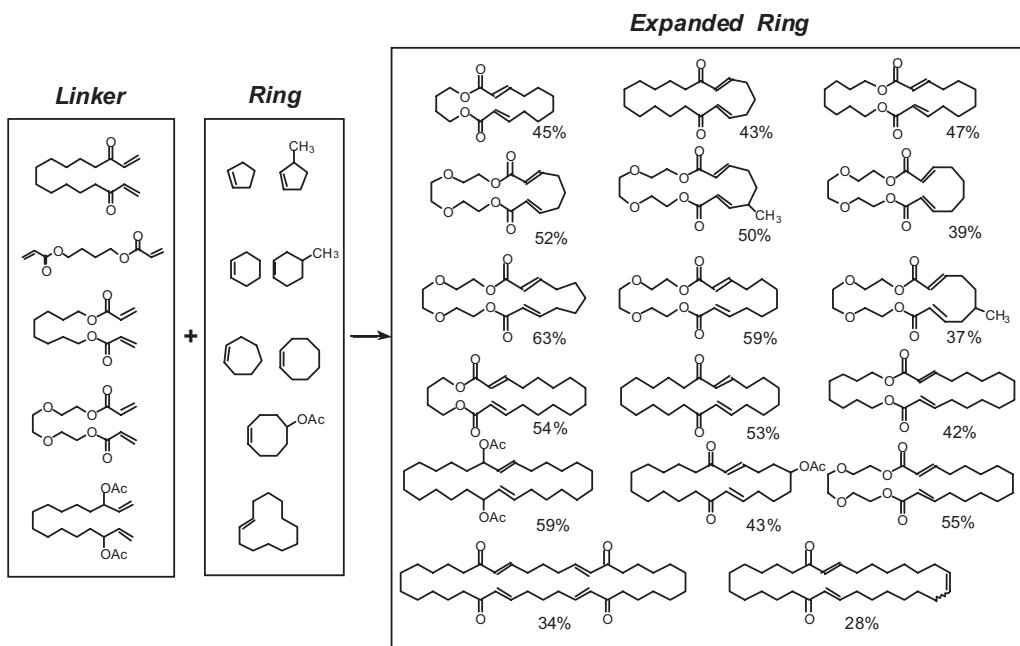
cyclohexene gave the poorest yield, even though one might have expected a yield comparable to if not better than that of cyclopentene. However, cyclohexene requires a different mode of the ring expansion. Since cyclohexene will not undergo olefin metathesis reactions with catalyst **2**, the initial step is the formation of the enoic carbene, [Ru=CO₂R] *in situ*, which can ring-open cyclohexene (Scheme 2.7-6) [8, 15, 16]. Since the enoic carbene is less stable than **2** or other electron-rich alkylidenes, fewer catalytic turnovers are expected, which is reflected in a low yield (entry 6). Substituted cycloalkenes reacted in a similar way to produce substituted macrocycles (entries 10 and 11).

Other acyclic dienes that undergo selective cross-metathesis should also serve as partners in this expansion reaction. One such substrate, diallylic acetate compound **23**, yielded 59% of the product **24** under conditions similar to the acrylate reactions (entry 12). Although diallylic acetate **23** can undergo self-metathesis, the reaction with ring-opened cyclododecene is more favored. In this case, two potentially polymerizable substrates react to form the ring-expansion product when the reaction is carried out at low concentrations.

This methodology can be extended to the synthesis of macrocyclic ketones in a one-pot process. Using the tandem catalysis condition recently developed [17], 22-membered cyclic dione, 1,12-cyclodocosanedione **25**, was obtained in 48% isolated yield over two reactions in one pot (Scheme 2.7-7).



Scheme 2.7-7. One-pot synthesis of 1,12-cyclodocosanedione **25**.



Scheme 2.7-8. Macrocycle formation using ring-expansion reactions.

In summary, ring-expansion metathesis reactions are a unique method for the synthesis of various macrocycles, where the product distribution was controlled by varying the concentration and the stoichiometry of cycloalkenes. Although the yields of the ring-expansion products are moderate, as summarized in Scheme 2.7-8, this methodology provides an easy access to a library of macrocycles such as macrolactones and macrocarbocycles, whose ring sizes can be controlled by the judicious choice of substrates, stoichiometry, and concentration of readily available cyclic olefins.

References

- 1 For reviews and discussions on general RCM including macrocyclization, see Chapter 2.2.
- 2 For a review on macrocycle synthesis, see C. J. ROXBURGH, *Tetrahedron* **1995**, *51*, 9767.

- 3 C. W. LEE, T.-L. CHOI, R. H. GRUBBS, *J. Am. Chem. Soc.* **2002**, 124, 3224.
- 4 K. C. NICOLAOU, J. A. VEGA, G. VASSILIKOGIANNAKIS, *Angew. Chem. Int. Ed.* **2001**, 40, 4441.
- 5 U. VOIGTMANN, S. BLECHERT, *Synthesis* **2000**, 893. For reviews and discussion on tandem RCM, see also Chapter 2.4.
- 6 For discussions on ring expansion reaction, see M. HESSE, *Ring Enlargement in Organic Chemistry*, VCH, USA, **1991**.
- 7 A. K. CHATTERJEE, J. P. MORGAN, M. SCHOLL, R. H. GRUBBS, *J. Am. Chem. Soc.* **2000**, 122, 3783.
- 8 S. RANDL, S. J. CONNON, S. BLECHERT, *Chem. Commun.* **2001**, 1796.
- 9 J. P. MORGAN, C. MORRILL, R. H. GRUBBS, *Org. Lett.* **2002**, 4, 67.
- 10 C. W. LEE, R. H. GRUBBS, *J. Org. Chem.* **2001**, 66, 7155.
- 11 C. W. BIELAWSKI, R. H. GRUBBS, *Angew. Chem. Int. Ed.* **2000**, 39, 2903.
- 12 T.-L. CHOI, I. M. RUTENBERG, R. H. GRUBBS, *Angew. Chem. Int. Ed.* **2002**, 41, 3839.
- 13 A. FÜRSTNER, O. R. THIEL, L. ACKERMANN, *Org. Lett.* **2001**, 3, 449.
- 14 M. DELGADO, J. D. MARTIN, *J. Org. Chem.* **1999**, 64, 4798.
- 15 T.-L. CHOI, C. W. LEE, A. K. CHATTERJEE, R. H. GRUBBS, *J. Am. Chem. Soc.* **2001**, 123, 10417.
- 16 M. ULMAN, T. R. BELDERRAIN, R. H. GRUBBS, *Tetrahedron Lett.* **2000**, 41, 4689.
- 17 J. LOUIE, C. W. BIELAWSKI, R. H. GRUBBS, *J. Am. Chem. Soc.* **2001**, 123, 11312.

2.8

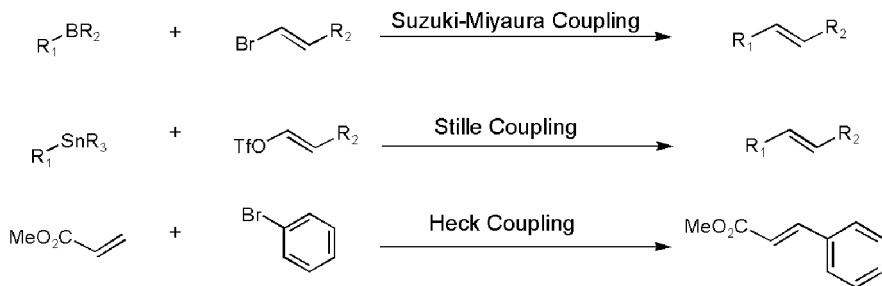
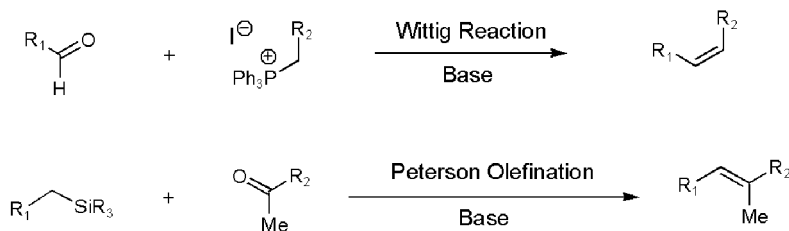
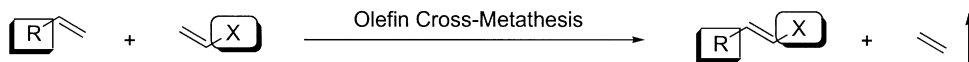
Olefin Cross-Metathesis

Arnab K. Chatterjee

2.8.1

Olefin Forming Cross-Coupling Reactions

It may be argued that the effective generation of diverse molecular structures via the efficient interconversion of functional groups underpins the foundations upon which the chemical sciences are built. In this regard, olefins represent a highly versatile functional group that can be readily generated and then reliably transformed into other synthetically useful functional groups, such as epoxides, aziridines and diols [1]. Alkenes are also a ubiquitous element in many complex organic molecules, and efficient installation of stereodefined olefins is a formidable synthetic challenge. In particular, the construction of stereodefined tetrasubstituted olefins remains a largely unsolved problem in organic chemistry [2]. On account of the functional utility of olefins, a variety of intermolecular and intramolecular alkene-forming procedures have been developed. For palladium-catalyzed methods, an activating group (such as an aryl or vinyl halide or triflate) is usually necessary for the reaction to proceed. These approaches, therefore, require considerable synthetic investment in the substrates (Scheme 2.8-1). Although very reliable, non-metal-mediated processes, e.g., the Wittig reaction, generally employ relatively reactive functional groups such as aldehydes and ketones. Consequently, protecting-group strategies are often required in order to mask these functional groups prior to their conversion to olefins. In contrast, however, a conceptually different approach to olefin formation by cross-coupling, namely, olefin cross-metathesis (CM), can be achieved through the exclusive use of olefins as starting materials. Furthermore, this protocol demands no change in oxidation state and the only significant reaction byproduct is a low-molecular-weight (i.e., volatile) olefin, most commonly ethylene. When comparing the olefination methods described in Scheme 2.8-1, the more commercially viable approaches, and those with the fewest waste byproducts, are the Heck [3] and CM reactions.

Palladium Catalyzed Methods:**Non-metal based methods:****Scheme 2.8-1.** Olefin formation by cross-coupling.**Scheme 2.8-2.** Direct cross-coupling with olefinic starting materials.**2.8.2****Olefin Metathesis and Selectivity Problems in CM**

Olefin cross-metathesis (CM), a strategy in which the olefins themselves are the reactive functional groups (Scheme 2.8-2), represents an attractive alternative to the other olefination methods described above. This methodology is particularly convenient on account of the many commercially available α -olefin sources. Moreover, the potential exists for CM to install natural product-relevant alkenes in synthetic structures, reminiscent of the fashion in which organic chemists have already utilized related ring-closing metathesis (RCM) protocols in the fabrication of naturally occurring macrocycles. Additionally, CM strategies provide an opportunity to append functional groups to olefins that can be used in subsequent transformations. In fact, CM may be able to install the appropriate functional groups required for the successful execution of the other olefin formation processes described in Scheme 2.8-1, i.e., silyl, stannyl, and boryl groups. Indeed, it is the rapid conversion of an α -olefin to useful functionalized synthons that provides CM with a unique opportunity, unlike RCM and ring-opening metathesis polymerization (ROMP) procedures, to install both structural and functional elements. The major

limitation in CM, however, lies in controlling elements of selectivity and represents a formidable challenge for the exploitation of CM as a reliable synthetic method.

Olefin metathesis is a thermodynamically controlled reaction that has become a highly versatile synthetic method for accessing alkene-containing compounds. In fact, olefin metathesis chemistry has had a profound impact in several areas of synthetic organic chemistry, including organometallic chemistry [4], polymer chemistry [5], and small molecule synthesis [6]. For example, ill-defined catalysts are used industrially in the CM synthesis of high-grade propylene from 2-butene and ethylene, as well as in the synthesis of neohexene. Furthermore, the synthesis of odd-carbon number internal olefins (C11, C13), from disproportionation of the non-C10–C14 fraction obtained from ethylene oligomerization, is an important application of CM in the Shell Higher Olefin Process (SHOP) [7]. Central to the accomplishments of the olefin metathesis reaction in organic synthesis is the utility of single-component transition-metal catalysts that exhibit organic functional group tolerance (Figure 2.8-1). If a transition-metal complex can perform selective reactions with olefins, then a wide variety of applications are possible. This proposition, however, represents a significant challenge since a plethora of metal-catalyzed processes are proficient at converting olefins into other functional groups, most notably a variety of oxidation procedures [1]. Despite this fact, however, the repeated demonstration of functional group tolerance of metathesis catalysts has endowed synthetic chemists with the confidence to subject highly valuable materials to these metathesis conditions. Obviously, such widespread application is vital for the success of any transition metal-based catalytic method. Historically, palladium-catalyzed cross-coupling reactions, such as Suzuki [8], Stille

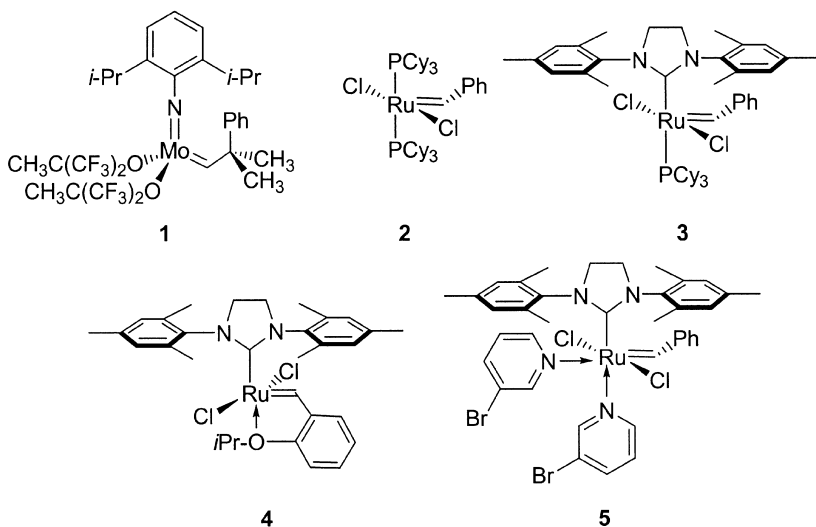


Fig. 2.8-1. Commonly Used Olefin Metathesis Catalysts

[9], and Heck [10] reactions, exhibit excellent functional group tolerance and have, therefore, been rewarded by numerous applications in total synthesis. In contrast, however, although the catalysts described in Figure 2.8-1 are prevalent in complex organic synthesis, these systems have not been extensively applied to CM as a consequence of unresolved problems of selectivity.

2.8.3

Metathesis Catalyst Overview

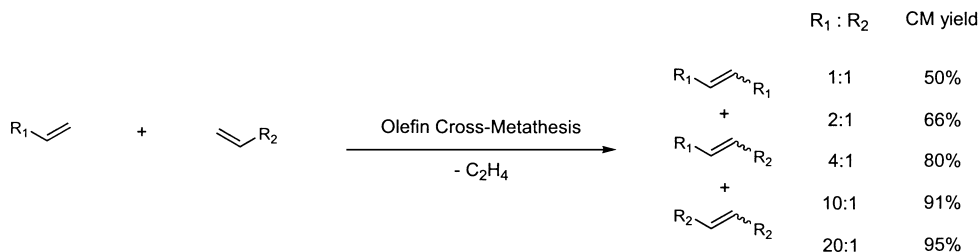
Several representative examples of the most commonly used single-component homogeneous olefin metathesis catalysts are shown in Figure 2.8-1. Earlier examples include the commercially available alkoxy-amido molybdenum carbene catalyst **1** [11] and ruthenium-based catalyst **2** [12], which have both been used in a variety of metathesis procedures. Interestingly, these two catalysts have developed a synergistic relationship in the metathesis literature over the last few years. For example, while **1** has demonstrated greater catalytic activity than **2**, it is more difficult to handle in the presence of air and water and can be poisoned by certain organic functional groups. It is for this reason that late transition-metal based systems, such as catalyst **2**, have been exploited in a variety of applications in organic chemistry, i.e., despite the fact that catalyst **2** generally exhibits lower metathesis activity than that of **1**, catalyst **2** is less susceptible to decomposition. The apparent tradeoff between functional group compatibility and activity, however, has been overcome with the recent development of catalyst **3** [13]. These imidazoylidene-based systems were developed in response to investigations that resulted in a more detailed understanding of the initiation processes for this family of catalysts. In addition, related systems bearing alkoxy (**4**) and pyridine L-type ligands (**5**) have been developed and subsequently employed in a variety of CM systems [14]. While still maintaining the desirable characteristics of early generation, late transition metal-based catalysts, namely, (1) ease of synthesis, (2) ease of handling, and, (3) functional group compatibility, catalysts **3–5** also possess greater electron density at the metal center as a consequence of σ -donation from the imidazoylidene ligand. This factor, coupled with a reduced π -back-bonding in imidazoylidene ligands, as compared with phosphine ligands, results in a greater preference for olefin binding and higher metathesis activity of these systems. Henceforth, these catalyst systems have been demonstrated to exhibit higher activity in metathesis applications than **1** or **2**, and their use in selective CM is discussed below. All four ruthenium-based catalysts have been widely used in ring-closing metathesis (RCM) [15], ring-opening metathesis polymerization (ROMP) [16], acyclic diene metathesis polymerization (ADMET) [17], and ring-opening/cross-metathesis (ROX) [18]. In addition, asymmetric variants of RCM [19] and ROX [20] have been reported with related ligand sets, illustrating another example of functional group tolerance in the context of chiral functionalized olefin formation. Obviously the issue of functional group tolerance, i.e., making olefins preferentially reactive in the presence of other functional groups such as halides, aldehydes, and alcohols, is

pertinent to all olefin metathesis procedures. The challenge in CM, however, is not merely the tolerance of these functional groups, as has been demonstrated so successfully in RCM and ROMP synthetic endgames, but the participation of these functionalities in determining CM selectivity. Finally, the fact that CM will be more commonly utilized early in a synthetic scheme, rather than other metathesis processes, compels such a process to provide a reliable and efficient method of accessing functionalized olefins that themselves are useful reagents for subsequent synthetic manipulations.

2.8.4

Selectivity Challenges in CM

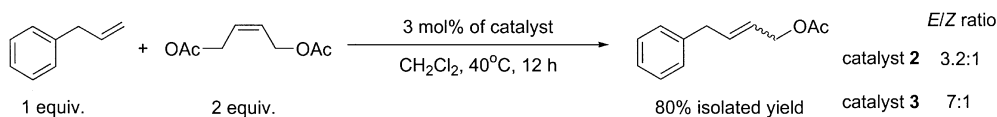
Despite the advances in olefin metathesis for RCM, ROMP, and ROX procedures over the past several decades, CM has received significantly less attention in the literature. In fact, the dimerization of olefins resulting from an unsuccessful RCM reaction is often where the status of CM has been relegated to within the metathesis literature. The broad applicability of CM cannot be mistaken, however, since it allows for the functional homologation of a variety of olefins in a single synthetic step and can draw upon a large pool of olefinic precursors. Indeed, numerous unfunctionalized olefinic precursors can be obtained from widely available petrochemical and oleochemical [21] sources. The conversion of these easily accessible unfunctionalized olefins to functionalized ones is, therefore, of great importance. Unfortunately, because CM is a simple intermolecular reaction governed by thermodynamics, several complications are inherent to the reaction. First, as a consequence of low catalytic activity and lack of selectivity in CM, a complex product mixture is often obtained (Scheme 2.8-3). For example, combining two olefins in equal stoichiometry that each react with the catalyst at similar rates would result in only 50% of the desired CM product. In addition, both undesired homocoupled products would also be obtained as the mass balance in the reaction. For the development of a synthetically efficient reaction, say to 90% conversion of a starting material to CM product, one would have to use nearly 10 equivalents of the desired CM partner. Furthermore, additional complications arise when, as a result of low catalytic activities, the reaction does not completely consume the terminal olefin starting materials. These factors make the CM reaction even more difficult



Scheme 2.8-3. Statistical distribution of CM products.

to execute, requiring the separation of the desired product from a total of five distinct olefin-containing reaction components. The persistence of unreacted starting olefin arises, in part, from the lower effective catalyst loading employed in CM reactions (relative to RCM protocols), stemming from the need to use an excess of one CM partner. Moreover, since intermolecular processes are involved in CM procedures, slower reaction rates also hamper catalyst activity. Greater catalyst activity, therefore, is central to advancing CM methodology, in that the consumption of all olefinic starting materials results in only three products, two homodimers and the heterocoupled CM product. In this regard, the high activity of catalyst **3**, and related catalysts **4** and **5**, has been instrumental in providing the reactivity necessary to consume all starting materials, thereby simplifying product mixtures and greatly increasing the utility of CM procedures. The ultimate goal in CM, however, is to provide the cross-metathesis product exclusively and preferably as a single olefin isomer. The issues of stereoselective CM and product-selective reactions are discussed in more detail later in this chapter.

Key to examining selectivity in CM reactions is to clearly understand the effect of secondary metathesis, i.e., the reentry of productive metathesis products into the catalytic cycle. Our investigations began by exploring the CM selectivity of allylic alcohols. For example, catalysts **2** and **3** are able to incorporate allylic alcohols with good to moderate stereoselectivity (Scheme 2.8-4). Specifically, the CM reaction between allylbenzene and an allylic alcohol equivalent affords the CM product in 80% isolated yield with either catalyst (**2** or **3**). The observed yields are consistent with those predicted statistically, i.e., 4 equivalents of allyl acetate are used in the reaction and CM product is obtained in 80% yield (Scheme 2.8-3). The reaction with catalyst **1**, however, provides a much higher amount of the *trans* olefin isomer, presumably as a consequence of the catalyst reacting with the CM product formed in the reaction, i.e., secondary metathesis. Efficient secondary metathesis occurs when all components in the reaction are equally accessible to the metal alkylidene complex, including the homodimeric and CM products. The increased *trans* ratio, therefore, simply reflects the higher activity of catalyst **3** toward the reaction products than that of catalyst **2**. Consequently, secondary metathesis of the CM product provides a metathesis-based isomerization route to the more thermodynamically favored *trans* isomer, making the reaction more synthetically useful. Furthermore, secondary metathesis processes account for the different stereoselectivities observed in these CM reactions. One main drawback, however, is that extensive secondary metathesis of the product does not go hand in hand with product selectivity of the CM reaction. As will be described below, eliminating secondary metathesis of the desired CM product allows for selective CM to occur if, in addition, the homodimeric products remain metathesis active and are consumed



Scheme 2.8-4. Olefin isomerization by secondary metathesis processes.

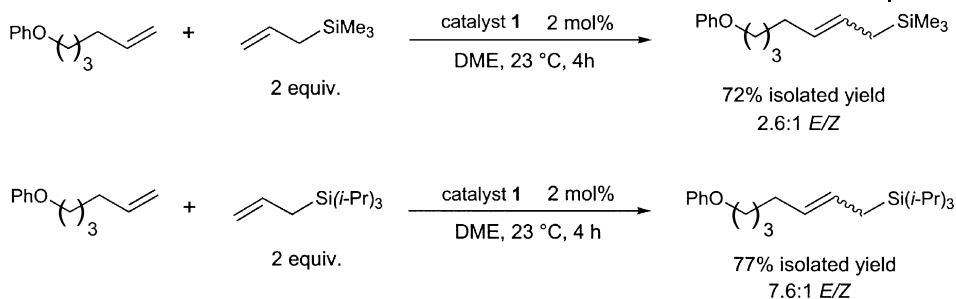
by secondary metathesis pathways. The most important discoveries in CM methodology, therefore, are those reactions that provide for selective formation of the CM product while also furnishing high stereoselectivities of the desired product.

The largely unresolved issues of olefin stereoselectivity and CM product selectivity have made CM a less developed synthetic method compared to ROMP, ROX, and RCM. A recent example discusses allene homodimerization using catalyst 2; however, the reaction has limited substrate scope and is hampered by the formation of significant quantities of side products resulting from polymerization [22]. The development and exploitation of selective olefin CM is still in its infancy. In the first part of this chapter, three distinct selectivity issues will be addressed, namely: (1) stereoselective olefin formation, (2) cross-coupling product selectivity controlled by the elimination of homodimerization pathways, and (3) olefin chemoselectivity in complex organic molecules. By considering and studying these aspects of selectivity in CM, synthetic chemists have recently become more comfortable in employing CM protocols in complex organic molecule syntheses, and this aspect will be the topic of discussion in the second part of this chapter.

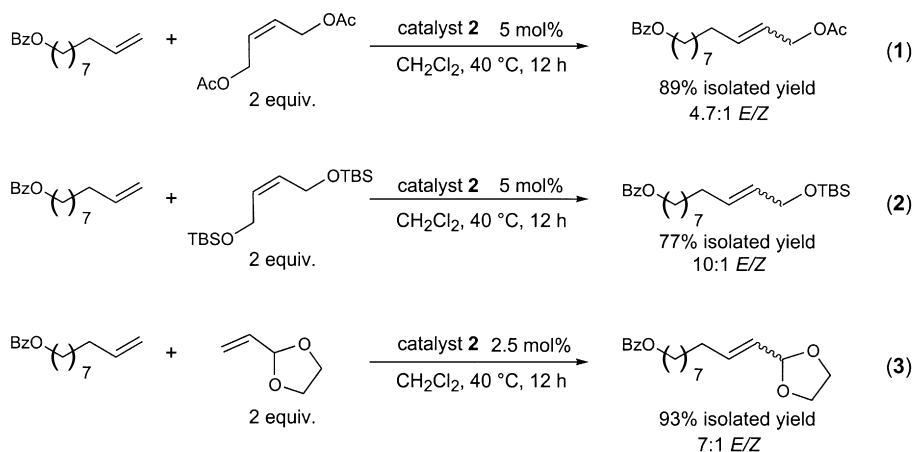
2.8.5

Stereoselective CM Reactions

Although olefin stereoselectivity is an issue in all metathesis reactions, prior to CM processes it was only pertinent to the RCM of large rings (>8 carbons) and in the backbone structure of ROMP-derived polymers. In CM, however, the issue of olefin stereoselectivity is centrally important to the utility of the method. As there is no general catalyst solution for the formation of *cis* olefins in a CM reaction, one approach to addressing this problem relies upon the use of removable tethers such that a RCM protocol can be exploited as a means to generate *cis* olefins, followed by subsequent cleavage of the tethers. Several groups have adopted this RCM strategy as a method to template the formation *cis* olefins, followed by tether cleavage [23]. This method, however, is not applicable to the problem of selectively generating *trans* olefins, which is addressed below. To achieve *trans* olefin selectivity in a CM scheme, one approach relies upon the addition of steric bulk directly on the olefin at the allylic position. The first findings in this area were reported by Crowe et al. with regard to allylsilane CM reactions using catalyst 1 (Scheme 2.8-5) [24]. In general, enhanced *trans* selectivity was observed when larger silicon substituents were present in the olefinic starting materials. For example, whereas employing allyltrimethylsilane resulted in a product *E/Z* ratio of 2.6:1, allyltriisopropylsilane gave a 7.6:1 *E/Z* mixture when crossed with the same terminal olefin CM partner. Both reactions gave similar yields of the CM products. Collectively, these results represented the first example of remote stereocontrol in cross-metathesis procedures. Furthermore, the products from these reactions are useful for silane additions to carbonyl compounds (the Sakurai reaction) and represent one of the earliest examples of reagent synthesis using CM protocols. Similarly, allylic stereocontrol could be obtained by exploiting the sterics associated with various allylic

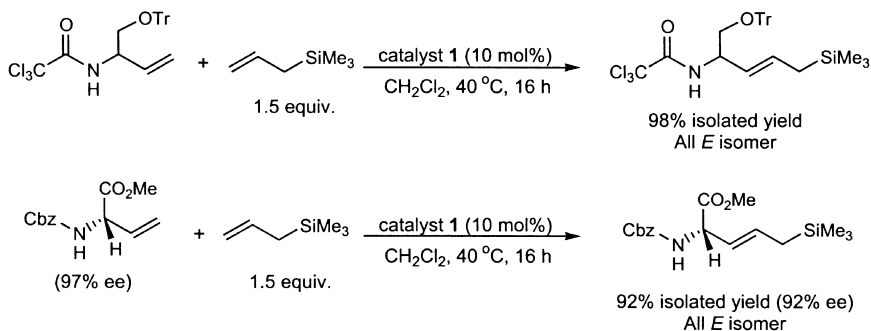


Scheme 2.8-5. Olefin stereoselectivity based on allylsilane substituents.

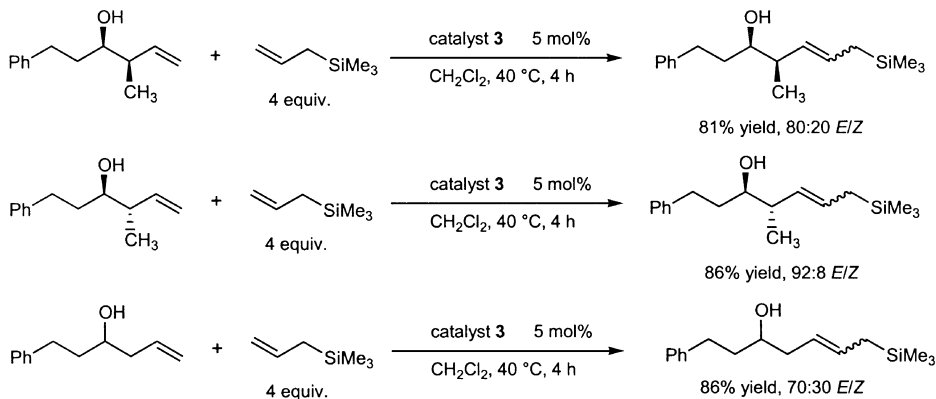


Scheme 2.8-6. Different stereoselectivity based on allyl-protecting groups with ruthenium catalysts.

alcohol-protecting groups in CM reactions mediated by catalyst **2** (Scheme 2.8-6) [25]. For example, the CM reaction of an α -olefin with an allyl acetate equivalent leads to a product *E/Z* ratio of 4.7:1, whereas the related allylic silyl ethers can enrich the *trans* isomer to a synthetically useful *E/Z* ratio of 10:1. Moreover, with substrates containing an allylic 1,2-diol it was determined that cyclic acetals were the most effective substituents for efficient CM reactions with a variety of α -olefin cross partners, affording (with catalyst **2**) products with a greater than 10:1 *E/Z* ratio [26]. One of the most significant results in this area is outlined in Scheme 2.8-6 and illustrates the use of acrolein acetals in CM reactions to yield protected α,β -unsaturated aldehydes. In this case, a higher amount of the *trans* olefin product is obtained than would be expected from the CM of simple unsubstituted olefins. Blechert and coworkers, however, demonstrated that heteroatom substitution from the allylic position improved *trans* selectivity of the CM products (Scheme 2.8-7). Perhaps the most impressive result of allylic stereocontrol from Blechert's work is observed with substituted allylic amines. Using catalyst **1**, Blechert demonstrated the first exclusively *trans*-selective CM reaction using purely steric contributions [27]. The authors also suggest the possibility that coordinating groups can have

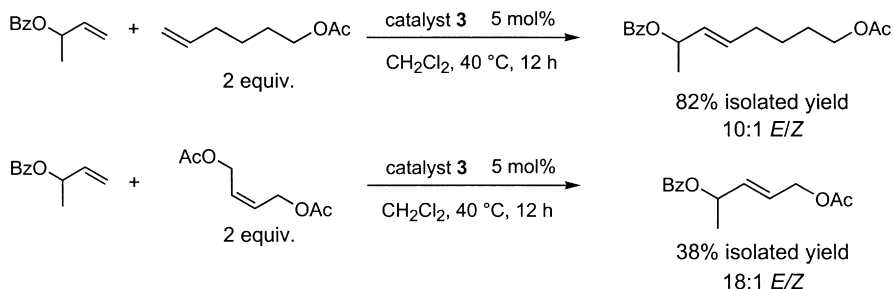


Scheme 2.8-7. Allylic substitution effects on CM olefin stereoselectivity.



Scheme 2.8-8. Relative stereochemistry effects on CM olefin diastereoselection.

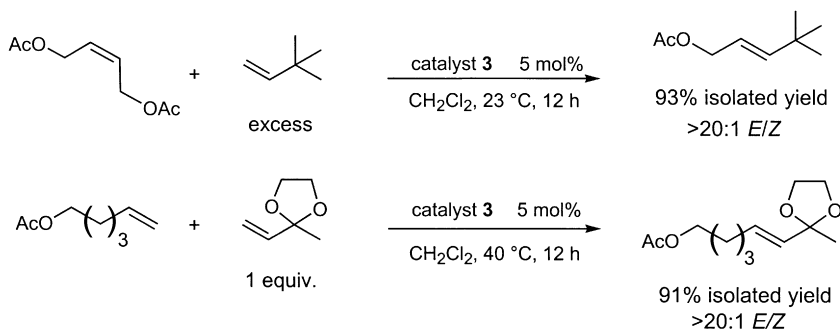
an impact upon both product- and stereoselectivity but are unable to provide a model for the observed selectivities. Regardless the completely stereocontrolled installation of a synthetically useful allylsilane is remarkable. In addition, the functional group tolerance of catalyst 1 is noteworthy, since minimal racemization of a highly epimerizable center is observed. This example also demonstrates excellent selectivity for the CM product over the corresponding homocoupled dimers. Recent work by Taylor and coworkers has demonstrated kinetic control in the CM of substituted homoallylic alcohols with allylsilanes using ruthenium catalyst 3 (Scheme 2.8-8) [28]. In this report, the authors show that secondary metathesis of the disubstituted CM products was not observed, thereby allowing for selective generation of the *trans* CM product. The most surprising result from this work, however, revealed that olefin diastereoselection could be governed by the relative stereochemistry of the substituents at the allylic and homoallylic positions. For example, an *anti* substitution pattern leads to a much higher proportion of the *trans* olefin in the product mixture. Indeed, the ability to use existing stereocenters to direct olefin stereoselectivity in CM reactions is an important application of this methodology.



Scheme 2.8-9. Effect of CM partners with secondary allylic alcohols.

Stereochemical relay from the allylic and homoallylic positions to the newly formed olefin is largely unprecedented. Furthermore, the presence of substituents aids *trans* selectivity, since the *E/Z* ratio falls to 70:30 without any allylic substituents present, similar to what was previously observed. These examples collectively demonstrate how allylic substitution can assist in the formation of *trans* olefins. The Caltech group has reinvestigated the role of allylic substitution in CM using the more active imidazolide catalysts, such as **3**, focusing in particular upon the inherent stereoselectivities observed in the CM of secondary and tertiary allylic alcohols. Catalyst **3** provided enhanced, and in some cases, complete *trans* olefin selectivity with these substrates. For example, the addition of a methyl group at the allylic position (Scheme 2.8-9) leads to much greater *trans* selectivity (10:1 *E/Z* ratio), compared to the 4.7:1 *E/Z* ratio that is obtained with a primary alcohol (see Scheme 2.8-6). Subsequently, the reactions of these secondary allylic alcohols with other allylic heteroatom-containing substrates was examined, and it was found that the *trans* selectivity was enhanced when another allylic-substituted olefin was used in the reaction. It is interesting to note, however, that the reaction yield decreases, indicating a possible match in product selectivity between these two partners, i.e., there is a significant amount of competitive homodimerization.

Additionally, during the course of earlier studies with catalyst **2**, it was found that substrates containing fully substituted allylic carbons (quaternary centers) did not participate in CM [25]. In contrast, however, the greater activity of catalyst **3** allows for the CM reaction between olefins bearing quaternary allylic carbons and α -olefins to be studied. The excellent stereoselectivities observed in CM with these substrates were anticipated from the earlier work (Scheme 2.8-10). Moreover, these reactions are useful because they are able to install highly substituted carbon atoms in a stereodefined manner [29]. For example, simple homologation of an olefin with a *tert*-butyl group proceeds in excellent yield of the CM product with only the *trans* isomer observed. Finally, the homologation of an α -olefin with the cyclic acetal of methyl vinyl ketone (1:1 substrate stoichiometry) can provide the CM product in excellent yield. These examples demonstrate the unique control of product and stereoselectivity in CM processes based upon purely steric considerations. Therefore, these early examples show that *trans* olefin selectivity could be achieved with minimal secondary metathesis since these products cannot be



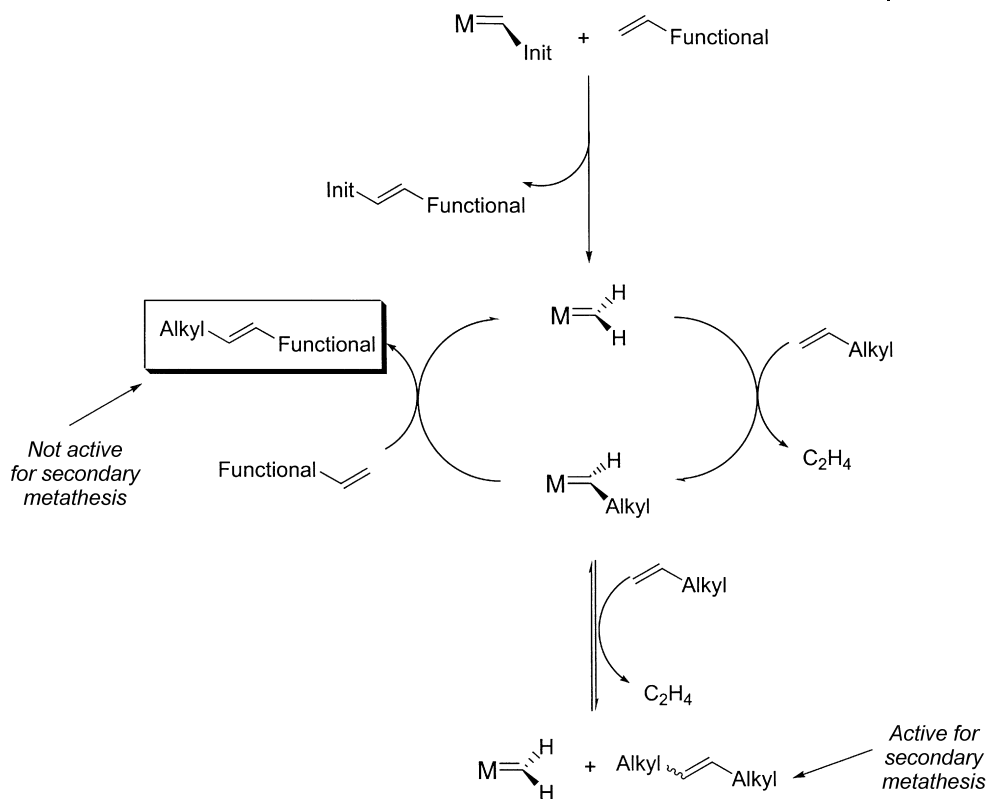
Scheme 2.8-10. Quaternary allylic carbons in CM with ruthenium catalyst **3**.

readily scrambled when re-subjected to the reaction conditions. Overall, the results described so far offer a fair number of *trans*-selective CM reactions that provide synthetically useful diastereoselectivities.

2.8.6

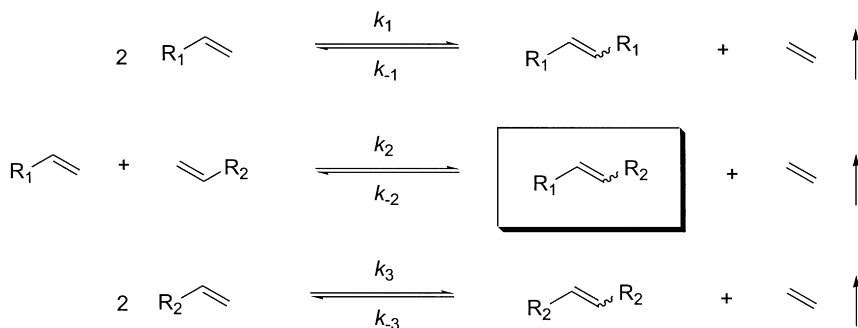
Product-Selective Reactions by CM

Product selectivity is a central issue in CM and is arguably the most important selectivity issue because it dramatically affects reaction and catalyst efficiency. Product selectivity in CM revolves around improving the yield of the CM product relative to homodimer formation, as described in Scheme 2.8-3, thus deviating from the expected statistical distribution. Limiting the formation of homocoupled product is particularly challenging in CM since there is no inherent orthogonality in the reactive functional groups present in the coupling partners, unlike the other cross-coupling methods described in Scheme 2.8-1. If the statistical distribution of heterocoupled and homocoupled olefin products can be overcome, however, then the ability to use simple olefinic starting materials, in equal stoichiometry, would be an extremely useful methodology for synthetic chemists. Furthermore, limiting the equivalents of CM partners in a selective CM process also reduces the resultant catalyst loadings by eliminating unproductive homodimerization pathways. Generally, the two ways in which homodimerization can be prevented are by altering either (1) the electronic or (2) the steric parameters associated with the CM partner. One method to limit dimerization, reported by Blechert et al., relies upon the binding of one olefin to a polymeric support to suppress its homodimerization, thereby increasing CM efficiency using catalyst **2** [30]. This result was rationalized as being a consequence of slow diffusion of the polymer-bound olefins, thus limiting their potential for homodimerization. Tethering did not, however, completely suppress unwanted homodimerizations, a phenomenon also recently reported by Tang and Wareing [31], and still required a large excess of one olefin, as is commonplace in solution-phase reactions. Therefore, simple attachment of one cross partner to a solid-support is not an efficient method through which one can achieve highly product-selective CM reactions.



Scheme 2.8-11. Proposed reaction pathway in selective cross-metathesis.

In product-selective CM reactions, the underlying implication is that one CM partner, such as an α -olefin, would provide a resting-state metal carbene. Therefore, the other CM partner, such as an electron-deficient olefin, would react in only a productive manner to give the desired CM product. Consequently, an α -olefin can rapidly dimerize before reacting with an electron-deficient olefin cross partner to form a CM product that is less accessible to subsequent secondary metathesis reactions. Differences in the rates of these processes allow for selective formation of the CM product, as depicted in Scheme 2.8-11. There are several important conditions, however, that must be met for successful selective CM to transpire. First, a catalyst system must sufficiently react with an α -olefin, and its dimer, on a timescale wherein productive CM with a second olefin can occur. The second condition is that the functionalized olefin CM partner does not dimerize, or it undergoes a slow dimerization relative to the formation of CM product. This constraint can be accomplished by adding electron-withdrawing groups to the olefin, thereby decreasing its reactivity toward an electrophilic carbene center. Another strategy to discourage homodimerization relies upon the addition of steric bulk at the allylic and homoallylic positions. Additionally, there is a significant amount of organo-



Scheme 2.8-12. Equilibria involved in olefin cross-metathesis.

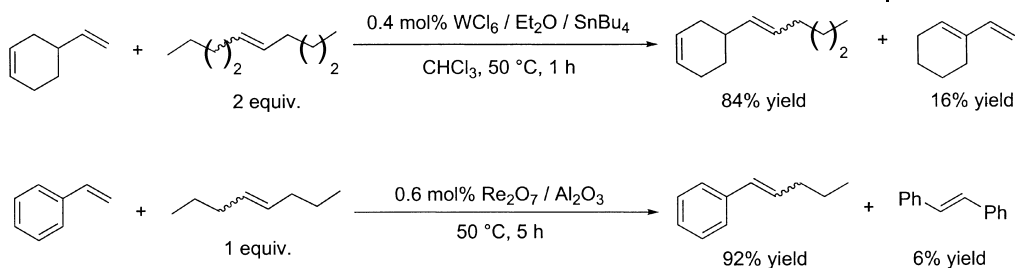
metallic chemistry that enables one to compare relative stabilities of propagating carbene species, thus allowing for the prediction of possible productive, selective reactions.

The relative rates of the homodimerization reactions are a major factor in product-selective CM reactions. In general, cross-metathesis reactions are driven to the desired product by using an excess of the more readily available cross partner. Most other efficient cross-coupling strategies, however, use differentiated functionalities, such as a vinyl stannanes and an alkyl chloride in Stille couplings, to allow for equal stoichiometry of reactants in the reaction. Nonetheless, under certain circumstances, cross-metathesis reactions can be highly efficient even when using equal stoichiometries of reactants. In a cross-metathesis reaction, there are three equilibria and six rate constants (Scheme 2.8-12). If the rates of all the reactions are similar, or if the reaction is allowed to proceed for a long period, the expected statistical ratios are obtained, with a near 50% yield of the cross product. If, however, one olefin, as a consequence of either steric or electronic factors, reacts to form the homodimer at a slower rate (k_3) than the other reactions, such that ($k_1, k_{-1}, k_2 \gg k_3$), and all the possible ethylene is removed from the system, such that all terminal olefins are consumed, then only the cross product is produced. These reaction conditions would therefore allow for much greater yields than the statistically predicted 50% CM product, since the only pathway for loss of ethylene from the R_2 -containing olefin is by cross-metathesis with an R_1 olefin.

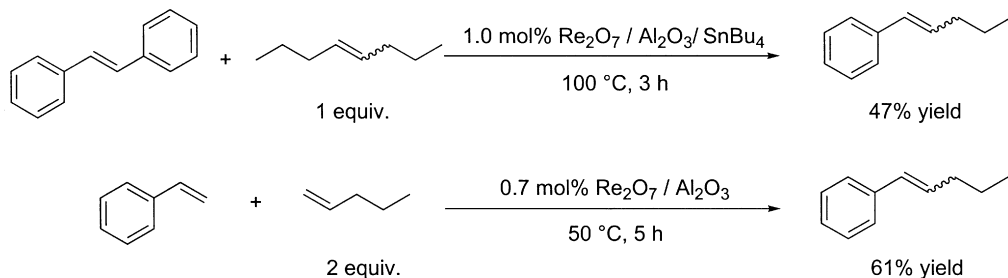
2.8.7

Styrene CM Reactions

The analysis of relative reaction rates is important in understanding why certain CM partners selectively produce the CM product. While this analysis has only been recently reported by the Caltech group, several previous reports in the literature have demonstrated product-selective CM. For example, the first reports of allylic-substituted olefins and electron-deficient olefins participating in product-selective CM were reported by Warwel and Winkelmüller in their homologation of terminal



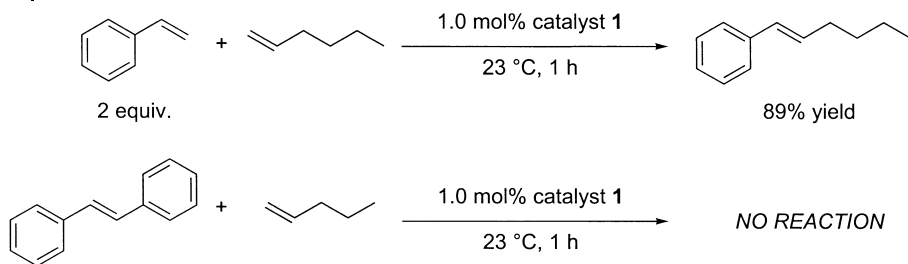
Scheme 2.8-13. First product-selective CM with ill-defined catalysts.



Scheme 2.8-14. Internal olefins in styrene CM with ill-defined catalysts.

olefins with styrene (Scheme 2.8-13) [32]. They were able to demonstrate that both electronic (styrene) and steric (allylic substitution) factors can govern CM product selectivities. Used in alkyl benzene synthesis, heterogeneous catalyst systems of $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$, among others, were employed in reactions between symmetrical unfunctionalized olefins and either 4-vinylcyclohexene or styrene. Unfortunately, in the case of the homogeneous $\text{WCl}_6/\text{SnBu}_4$ catalyst system, olefin migration led to the formation of the isomeric 1-vinylcyclohexene and, therefore, did allow for excellent CM efficiencies beyond simple statistical mixtures. In addition, the stereoselectivities of these reactions were not reported, making it unclear what effect a secondary allylic carbon has on olefin stereoselectivity.

The non-statistical product distribution obtained by Warwel and Winkelmüller illustrates the first product-selective CM reaction. In this case, the selectivity arises from the slow dimerization of styrene to stilbene. Furthermore, the authors demonstrated that stilbene participation in CM reactions with internal olefins required higher catalyst loadings and harsher reaction conditions and led to lower conversions versus styrene (Scheme 2.8-14). These results demonstrate that, by re-subjecting an isolated homodimer (such as stilbene) to the reaction conditions, one can determine whether selective CM is in operation. Furthermore, it was observed that higher yields of the desired CM product were obtained starting from the symmetrical internal olefins (92%) rather than their terminal olefin counterparts (61%). The authors concluded that several catalytic cycles were consumed by the dimerization of aliphatic olefins, rather than in productive CM, leading to lower yields. This work demonstrates the advantages of using disubstituted olefinic



Scheme 2.8-15. Styrene CM with molybdenum catalyst 1.

starting materials rather than their α -olefin counterparts. It was later observed that the CM of internal olefins with allylic alcohols, catalyzed with **2**, was also more efficient than the analogous reaction using the corresponding terminal olefins [25]. Subsequently, styrene CM reactions have been reinvestigated within the last several years using well-defined homogeneous catalysts. Molybdenum-based catalysts provided different results from those obtained by Warwel using ill-defined catalyst systems. Schrock and coworkers discovered different rates of styrene dimerization using different ligand sets on molybdenum [33]. Crowe and coworkers demonstrated concurrently the kinetic CM between α -olefins and styrenes using catalyst **1**, to afford, stereoselectively, *trans* olefins (Scheme 2.8-15) [34]. Furthermore, this reaction is unique because they determined that stilbene was not an active CM partner, unlike with the earlier ill-defined catalysts. Crowe and Zhang also discovered that the reaction between styrene and an internal olefin dimer exclusively produces the CM product, but at a much slower rate than the CM reaction between styrene and an α -olefin. These experiments suggest an unprecedented, highly selective process, where *neither* homodimer is formed and only the CM product is obtained, in which k_2 is much faster than all the other rates (Scheme 2.8-12). Only the elimination of one homodimerization pathway, however, is required to achieve product-selective CM, as demonstrated with 1,1-disubstituted olefins and α,β -unsaturated carbonyl compounds described below.

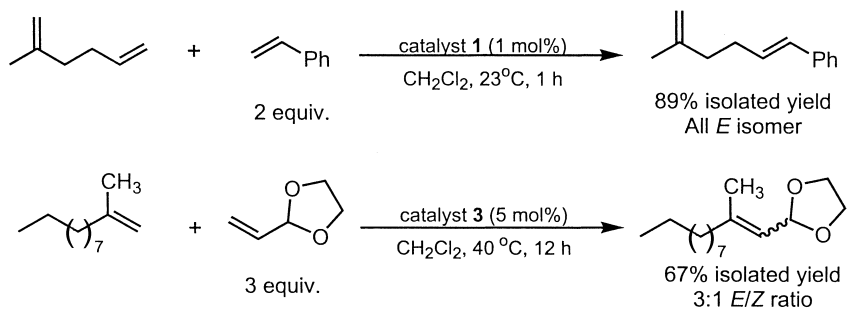
Understanding relative reaction rates is essential to developing selective CM reactions. In particular, the advantageous use of internal olefins in CM, as initially described by Warwel and Winkelmüller, has also been exploited in several other catalyst systems. For example, concurrent with work on styrene CM, Banasiak examined the role of internal olefins in insect pheromone synthesis using ill-defined tungsten Fischer carbene complexes [35]. Several important observations were made from this work. For example, it was observed that the removal of ethylene increases both catalyst efficiency and *trans* stereoselectivity by providing an entropic driving force in the reaction. The improved stereoselectivity may arise from the secondary metathesis of the products, leading to the more thermodynamically favorable *trans* olefin. In addition, it was found that the use of internal olefins, instead of the corresponding α -olefins, allowed for lower catalyst loadings, greater CM product selectivity, and higher *trans* diastereoselectivity. These results were also corroborated at Caltech using catalyst **2**, in addition to comparison with

the CM of allylic acetates wherein internal olefin diacetates provided slightly higher CM yields and *trans* selectivities [25]. This improvement in CM efficiency can be attributed to a lower stability of the intermediate methylene carbene, relative to alkyl-substituted carbenes, as indicated by independent mechanistic studies. The formation of an intermediate methyldiene complex occurs less often with the use of one set of symmetrically disubstituted olefins [36]. This aspect of the work also provides an example of the advantage of using single-component catalyst systems in CM, since intermediate catalytic species can be independently synthesized and studied. One case where our knowledge of organometallic intermediates has been applied to improve synthetic methodology is with allyl acetate CM reactions that are mediated with catalyst **2**. The increased catalyst stability attained with internal olefins prolongs the lifetime of the catalyst, and, therefore, can result in greater secondary metathesis activity, thereby improving *trans* stereoselectivity, an outcome that is similar to what Banasiak observed in the pheromone synthesis described above. It is clear that CM product selectivity and olefin stereoselectivity issues must be properly addressed to develop synthetically useful CM processes. While ill-defined catalytic systems were not very tolerant of functional groups, underwent unwanted side reactions (such as olefin isomerization), and did not provide much opportunity for mechanistic studies, they did provide some insights into achieving selective CM processes by judicious choice of CM partners. Two instances where product selectivity has been achieved by understanding the proper choice of CM partners are in the CM of 1,1-disubstituted olefins and α,β -unsaturated carbonyl-containing olefins. The next two sections of this chapter address product selectivity with these two substrate classes.

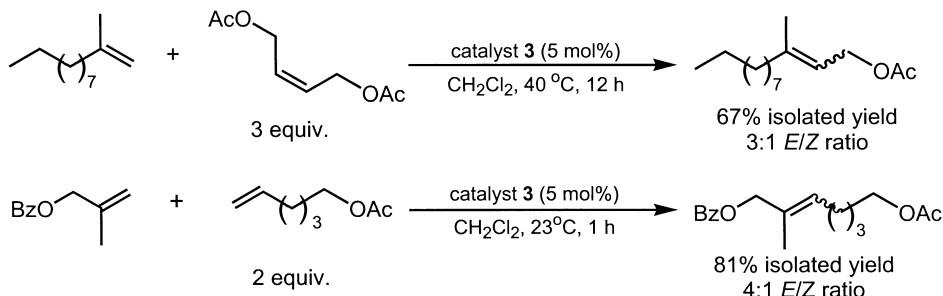
2.8.8

Trisubstituted Olefin Synthesis by CM

While a variety of trisubstituted olefins have been synthesized by ring-closing metathesis (RCM) reactions, the synthesis of trisubstituted olefins by CM had not been reported until recently. Wagner et al. reported the ADMET polymerization of 2-methyl-1,5-hexadiene with catalyst **1** to produce polymers of moderate molecular weight that had trisubstituted olefins in the polymer backbone [37]. The polymer backbone did not contain disubstituted or tetrasubstituted olefins that would represent either head-to-head or tail-to-tail coupling. In contrast, under CM conditions, Crowe et al. reported that 1,1-disubstituted olefins were not reactive for CM with styrene using catalyst **1** (Scheme 2.8-16) [34]. For example, in the presence of a 1,1-geminally-disubstituted diene, only the α -olefin is active for CM. Subsequently, however, the Caltech group was able to observe the first example of intermolecular CM between geminally disubstituted olefins and α -olefins to generate trisubstituted olefinic products using catalyst **3** [38]. Our studies began with the use of 2-methyl-1-undecene as an unfunctionalized geminally disubstituted olefin in CM reactions with vinyl dioxolanes (Scheme 2.8-16). This procedure provides direct access to a protected trisubstituted α,β -unsaturated aldehyde in moderate

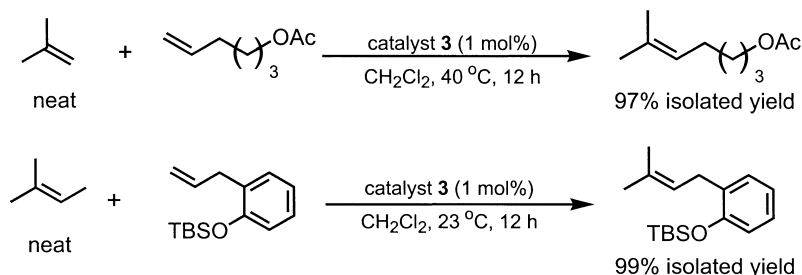


Scheme 2.8-16. Olefin cross-metathesis with 1,1-disubstituted olefins.



Scheme 2.8-17. Role of allylic functionality in 1,1-disubstituted olefin CM.

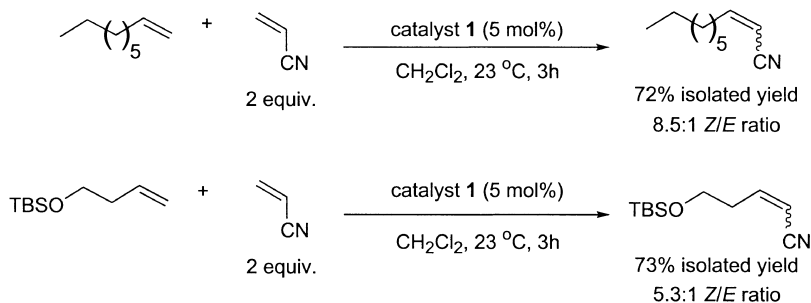
yields with moderate stereoselectivity. We found that certain homodimers, such as the dioxolane homodimer, were not as active for subsequent CM as was the terminal dioxolane equivalent. In this case, maintaining a low concentration of α -olefin reduces the formation of an unreactive homodimer and increases the yield of CM product as outlined in Scheme 2.8-12. For example, in a case where k_{-1} and k_2 are small relative to k_1 , one needs to maintain a low concentration of the R_1 olefin to increase its participation in selective CM. Unlike the reactions in which vinyl dioxolane is the CM partner, some α -olefin partners such as 1,4-diacetoxy-*cis*-2,3-butene and allyl acetate can be interchangeably used in CM (Scheme 2.8-17). This fact demonstrates that k_1 and k_{-1} are greater than k_2 , the rate constant for the productive formation of CM product. Functionalized disubstituted olefins, such as one bearing two allylic benzoate groups, also proved to be excellent substrates for this reaction and showed improved yields relative to that observed with substrates possessing only pure alkyl substitution (Scheme 2.8-17). Finally, it should be noted that in all these reactions, the disubstituted olefin does not undergo homodimerization, enabling, in theory at least, quantitative recovery of unreacted starting materials. Eventually, it can be argued that more active catalysts may be able to perform this dimerization, allowing for the synthesis of tetrasubstituted olefins. To achieve selective reactions affording trisubstituted olefins, however, it would be more efficient to use a less active catalyst and thereby eliminate one homodimerization pathway.



Scheme 2.8-18. Isoprenoid synthesis by olefin cross-metathesis.

Unfortunately, however, we were relatively disappointed with the olefin diastereoselectivity and moderately high catalyst loadings and reaction temperatures required in these reactions. Therefore, we wanted to investigate the use of symmetrical 1,1-geminally disubstituted olefins. In fact, we have been able to affect the convenient CM of symmetrical 1,1-disubstituted olefins with a variety of CM partners. Of particular interest is an isoprenoid synthetic route via the homologation of α -olefins with isobutylene or 2-methyl-2-butene using catalyst **3** (Scheme 2.8-18) [39]. The reactions of a variety of olefins with isobutylene provide excellent CM yields. We were particularly pleased with these reactions since the prenyl groups generated are a ubiquitous structural element in a variety of natural products and are now readily accessible in a highly selective CM reaction. The CM efficiency is surprisingly good, since the catalyst loadings are very low relative to the amount of bulk olefin in the reaction, with an effective catalyst loading of 0.0001 mol%. Furthermore, the inability of the 1,1-disubstituted olefins to readily homodimerize allows for them to serve as both a reaction solvent and an effective CM partner. These factors allow for selective CM reactions in which the trisubstituted olefinic products are obtained in excellent yields. The substrate scope in these CM reactions is quite general, including α -olefins and, in particular, a phenolic allylbenzene, where CM is a convenient alternative to aromatic Claisen chemistry that would initially require the synthesis of a tertiary phenoxy ether. In fact, we were pleased to find that this method has been applied in an allyl to prenyl conversion in the synthesis of the core of garsubellin A [40]. In a related synthetic approach, a tandem olefin isomerization/ethylene CM reaction has been used to convert an allyl group to a vinyl group in the total synthesis of (–)-tuberostemonine [41]. These two examples demonstrate the ability of olefin CM reactions to accomplish structural group interconversions, utilizing in particular its ability to form highly substituted olefins.

As illustrated above, styrene CM represents one of the first examples of the participation of π -substituted olefins in intermolecular CM reactions. Another class of π -substituted olefins that participate in CM with catalysts **3**–**5** is the α,β -unsaturated carbonyl olefins. Our work in this area has opened up several new avenues for CM reactions in organic synthesis and has also furnished a better understanding of the factors involved in selective CM.

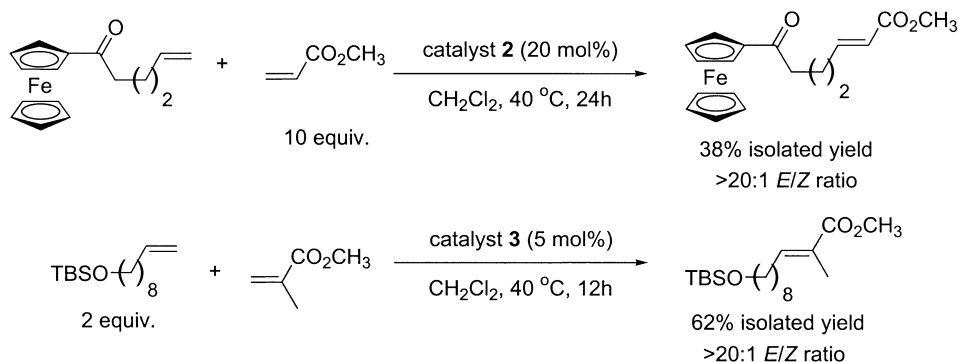


Scheme 2.8-19. Acrylonitrile CM with molybdenum-based catalysts.

2.8.9

Electron-Poor Olefins in CM

The generation of olefins with electron-withdrawing functionality, such as α,β -unsaturated aldehydes, ketones, and esters, remains an important transformation in organic chemistry. The ability to synthesize these functionalities without the direct use of carbonyl-containing compounds and Wittig reagents would be valuable. One of the initial reports in this area, by Crowe and Goldberg [42], showed that acrylonitrile participated in a cross-metathesis reaction with a variety of α -olefins using catalyst **1** (Scheme 2.8-19). Interestingly, this work provided one of the few examples where *cis* olefins are selectively produced, as the CM products are not active for secondary metathesis isomerization to the *trans*-unsaturated nitrile compound. In addition, the homodimerization of acrylonitrile was not detected, demonstrating excellent product selectivity and resulting in a slightly higher yield (72%) than the statistical prediction (66%). Other α,β -unsaturated compounds such as enones and enoic esters, however, were not compatible with molybdenum alkylidene **1**, thereby strictly limiting this methodology to acrylonitriles. However, ruthenium alkylidenes such as **3** and, more recently, the *N*-heterocyclic carbene catalyst **4** [43] have displayed unique new activity in CM reactions toward these previously metathesis-inactive substrates, namely, α,β -unsaturated carbonyl-containing olefins. There has been one report on the CM of acrylate esters with catalyst **2**, but the yield is low and requires high catalyst loadings (Scheme 2.8-20) [44]. In addition, a large excess of acrylate was required to provide any measurable amount of CM product. The homologation of terminal olefins with α,β -unsaturated carbonyls, however, has been efficiently accomplished using ruthenium alkylidenes such as **3**. The reaction exhibits excellent selectivity in terms of both product selectivity and stereoselectivity [45]. This result prompted the investigation of the use of a variety of α,β -unsaturated carbonyl-containing compounds in CM reactions (Table 2.8-1). The CM reaction between an allyl alcohol and a vinyl ketone works well, providing an example where α -olefins bearing functionality at the allylic position can be used (entry 3). A variety of allylic substituted α -olefins can be used in the reaction, affording only the *trans* olefin stereoisomer. For example, secondary (entry 4) and tertiary allylic alcohols (entry 5) can be used,



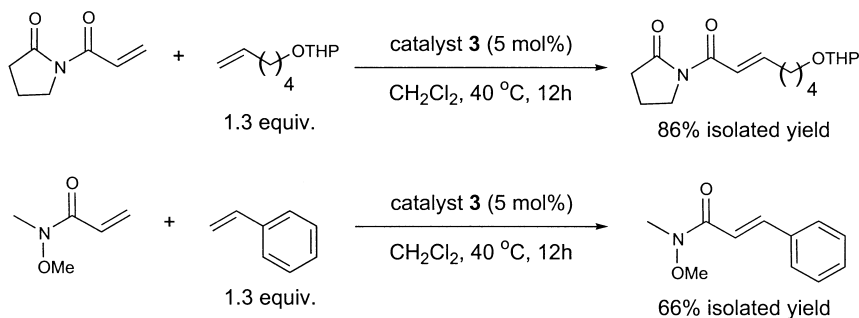
Scheme 2.8-20. Acrylate CM with ruthenium-based metathesis catalysts.

Tab. 2.8-1. Cross-metathesis reactions with unsaturated esters, aldehydes, and ketones^a.

Entry	CM partner	Unsaturated carbonyl	Equiv.	Product	Isolated yield (%)
1	TBSO-(CH ₂) ₇ -CH=CH ₂	CH ₂ =CH-CO ₂ CH ₃	0.5	TBSO-(CH ₂) ₇ -CH=CH-CO ₂ CH ₃	62
2	BzO-(CH ₂) ₇ -CH=CH ₂	CH ₂ =CH-CO ₂ CH ₃	2.0	BzO-(CH ₂) ₇ -CH=CH-CO ₂ CH ₃	91
3	AcO-CH=CH-OAc	CH ₂ =CH-C(=O)CH ₃	0.5	AcO-CH=CH-C(=O)CH ₃	81
4	HO-CH(CH ₃)-CH=CH ₂	CH ₂ =CH-CO ₂ Et	2.0	HO-CH(CH ₃)-CH=CH-CO ₂ Et	92
5	HO-C(CH ₃) ₂ -CH=CH ₂	CH ₂ =CH-CO ₂ <i>n</i> -Bu	2.0	HO-C(CH ₃) ₂ -CH=CH-CO ₂ <i>n</i> -Bu	95
6	AcO-(CH ₂) ₃ -CH=CH ₂	CH ₂ =CH-CHO	0.5	AcO-(CH ₂) ₃ -CH=CH-CHO	92
7	THPO-(CH ₂) ₃ -CH=CH ₂	CH ₂ =CH-COOH	0.8	THPO-(CH ₂) ₃ -CH=CH-COOH	100

^a Reactions with 3–5 mol% of 3.

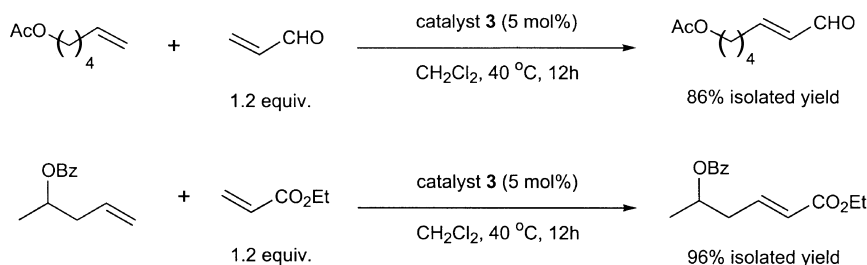
demonstrating that the reaction is amenable to allylic substitution of the substrates. Particularly noteworthy are the excellent yields attained with aldehydes (Table 2.8-1, entry 6) where the desired oxidation state can be directly accessed, a result that is in contrast with HWE chemistry in which the aldehyde is accessible only through further synthetic manipulations. Finally, acrylic acids are highly efficient substrates for CM reactions, providing quantitative yields of CM products



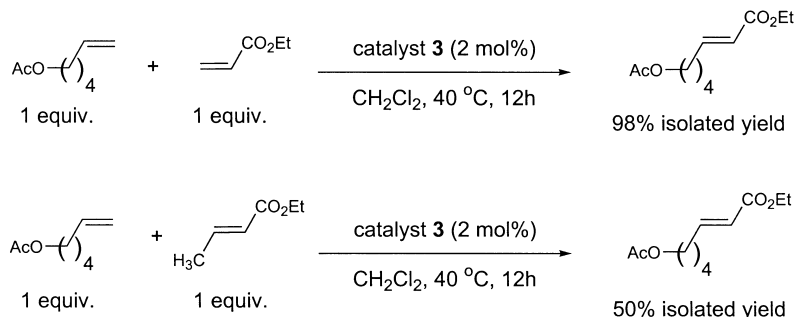
Scheme 2.8-21. Acrylamide CM with ruthenium imidazolydene catalysts.

requiring only a slight excess of α -olefin (1.2 equivalents) (Table 2.8-1, Entry 7). Similar CM reactivity has also been observed with acrylic amides (Scheme 2.8-21) [46]. For example, the simple homologation of α -olefins with vinyl oxazolidiones provides access to a variety of useful substrates. In addition, Weinreb amides were also demonstrated to be viable cross partners in these CM reactions using ruthenium initiator **3**. Two important results originated from this work. First, a variety of amide substituents were shown to have different activity in CM reactions, implying that turnover of the metathesis catalyst may be affected by the Lewis basicity and steric bulk associated with the amide carbonyl group. This type of chelating effect has important implications in catalytic efficiency, even in late transition metal complexes that are less Lewis acidic. The second important result from this work is the high efficiency of the CM reaction with styrene, thereby opening up a route to *trans* cinnamides. Work from this group has also demonstrated the potential for acrylate and vinyl ketone CM reactions with styrenes and π -conjugated heterocycles as an alternative to the Heck reaction [47]. In addition, CM between two different styrenes has been performed in low yields with catalyst **2** [48]. These results are in contrast to those reported by Crowe and coworkers, which indicated that, with molybdenum-based catalyst **1**, two π -conjugated olefins were not compatible in CM reactions as a consequence of similarities in electronics. With more active catalyst **3**, however, it was found that these types of reactions are, indeed, highly efficient, indicating that the electronic structure of the olefin does not alone govern selectivity in CM. It should also be noted that Kawai and coworkers have demonstrated the selective CM between styrene derivatives and vinylferrocene using catalyst **1**, demonstrating another example of CM between two different π -substituted olefins in moderate yields [49]. In summary, while there is not a great deal of explanation for the observed product-selective CM reactions, there is a fair amount of empirical information on product-selective CM reactions with electron-deficient olefins.

Next, we wished to further investigate the level of product selectivities in the reactions with α,β -unsaturated carbonyl olefins. Our hypothesis was that by using electron-deficient olefins, dimerization of these olefins should be slow relative to productive CM. We were able to test this theory by using a 1:1 stoichiometry in the CM reactions (Scheme 2.8-22). We found that both acrolein and acrylates could be



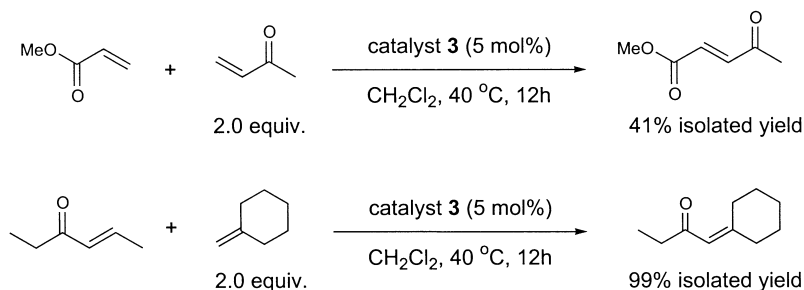
Scheme 2.8-22. Product-selective CM with ruthenium imidazolyldiene catalysts.



Scheme 2.8-23. Acrylate versus crotonate in CM with ruthenium imidazolyldiene catalysts.

used in slight excess to provide excellent CM reaction yields. Again, in the acrylate CM reaction, base-sensitive homoallylic substrates are excellent partners for CM. These reactions, therefore, represent alternative methods to Wittig olefination where the reaction can now be performed under neutral conditions and further demonstrate the orthogonality of olefin metathesis to other olefination methods. It should be noted that recent reports have expanded the range of catalysts that can perform acrylonitrile CM to include complexes **4** [50] and **5** [51].

We became interested in understanding which factors were responsible for such unprecedented selectivity in CM. For example, we knew that under certain reaction conditions, the acrylate dimerization was quite efficient but was much slower than the acrylate CM reaction with α -olefins. It was shown previously by Blechert et al. that propensity for dimerization is not the proper measurement for determining a candidate for selective CM with α -olefins, since certain olefins that can individually dimerize also participate in selective CM reactions [52]. We wished to investigate whether the CM products obtained in these selective reactions were accessible for secondary metathesis. Indeed, we found that these reactions did not scramble the productive CM reactions, i.e., there was no secondary metathesis. To further illustrate this important point, we carried out the reaction of ethyl crotonate under the optimized reaction conditions for acrylate CM and found that the CM reaction efficiency was dramatically lower (Scheme 2.8-23). Even though the entropically driven loss of a volatile gas (propylene) exists for crotonate CM partners, we found that the yield of CM product was reduced dramatically, i.e., by 50%. Therefore,

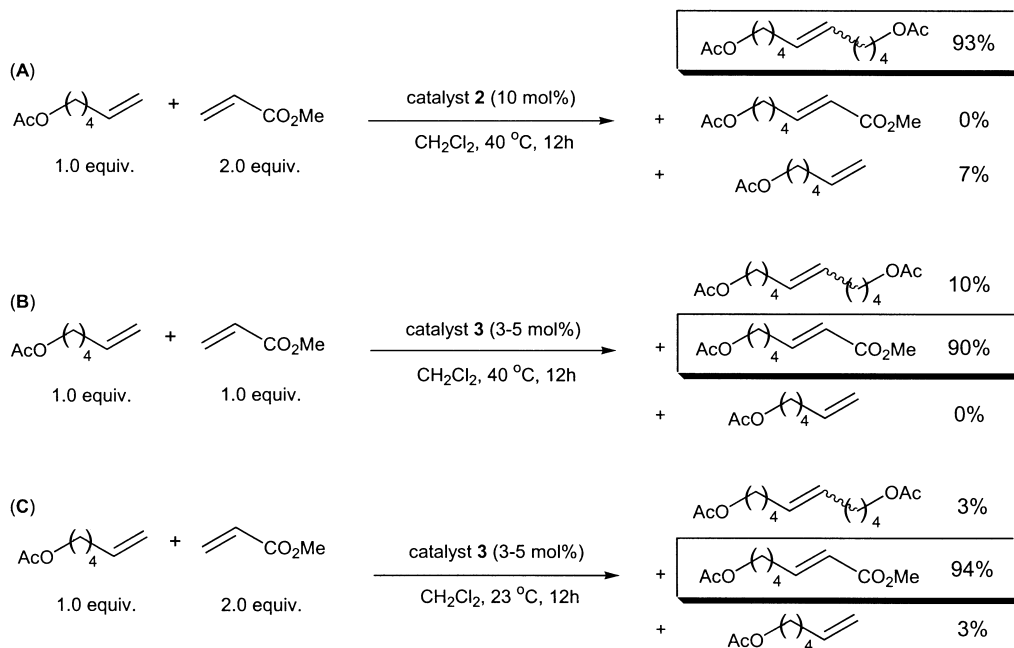


Scheme 2.8-24. Acrylate and enone CM with challenging partners.

the 1,2-disubstituted α,β -unsaturated carbonyl-containing olefins formed in these reactions are not readily accessible for secondary metathesis. Fortunately, this kinetic formation of CM products does not lead to low olefin stereoselectivity. This result is surprising, since many metathesis catalysts often provide *cis*-substituted olefins as a kinetic product, and is not clear why the *trans* olefin is formed as the initial stereoisomer in these reactions.

As the range of substrates for CM was being expanded, we also became interested in using more challenging terminal olefins as the CM partner. In fact, since these α,β -unsaturated compounds are useful synthons in organic chemistry, we wished to make some challenging substrates by CM, and the results are outlined in Scheme 2.8-24. For example, the homodimerization of acrylates proceeds in good yield (>75%) and the ability to carry out CM between two enones is possible, although the yields are modest (Scheme 2.8-24) [53]. In addition, a reaction between acrylates and 1,1-disubstituted olefins provides access to ketone Horner-Wadsworth-Emmons products in excellent yields. We were gratified to find that these substrates work well with catalyst 3, even though a twofold excess of the 1,1-disubstituted component is required for high CM conversions. This requirement is a consequence of either the electronic or steric demands of the reacting olefins, as neither olefin readily reacts directly with the metal catalyst.

In summary, several novel stereoselective CM reactions have been discovered that allow for the synthesis of highly functionalized olefins. The differences in reactivity trends between catalyst 2 and 3 are quite remarkable. For example, when considering the chemistry of α,β -unsaturated esters with terminal olefins, catalyst 2 simply performs the dimerization of the α -olefin component (Scheme 2.8-25a). Catalyst 2 is not inactivated upon the addition of an α,β -unsaturated ester (such as ethyl acrylate) but simply does not incorporate this olefin. This outcome is quite different from that observed with molybdenum catalyst 1 which is poisoned for any metathesis upon addition of acrylates [42]. Crowe and Goldberg explain this observation in terms of a possible heteroatom coordination of the acrylate to the molybdenum center. When catalyst 4 is used in the same reaction, however, a highly product-selective CM reaction between the two olefins occurs. Furthermore, the olefins may be present in equal stoichiometry (an excess of one is not required), and the product is formed with exclusively *trans* olefin stereochemistry (Scheme 2.8-25b). This reaction does contain a background dimerization of the



Scheme 2.8-25. Catalyst and temperature effects on product distribution in acrylate CM.

acrylate component, however, that accounts for the other 10% of the material in the reaction. This product may be formed upon secondary metathesis of the productive CM product and by a direct acrylate dimerization pathway. Nonetheless, both of these processes are slower than the productive CM reaction, and thus only small amounts of this byproduct are observed in the reaction. While in the process of optimizing this reaction, we hypothesized that using a lower reaction temperature may result in an increase in CM product selectivity. In fact, when we performed the CM at room temperature, there was no acrylate dimerization product, and a higher yield of the CM product was obtained (Scheme 2.8-25c). This procedure is highly efficient since all of the side products formed in the reaction (starting acrylate, α -olefin, and α -olefin dimer) can be recycled in subsequent CM reactions. In contrast, when an acrylate dimer is formed, it cannot be efficiently recycled in a subsequent CM procedure. The work done with electron-deficient olefins over the last 10 years has provided some highly valuable reactions for the synthesis of functionalized olefins by CM.

2.8.10

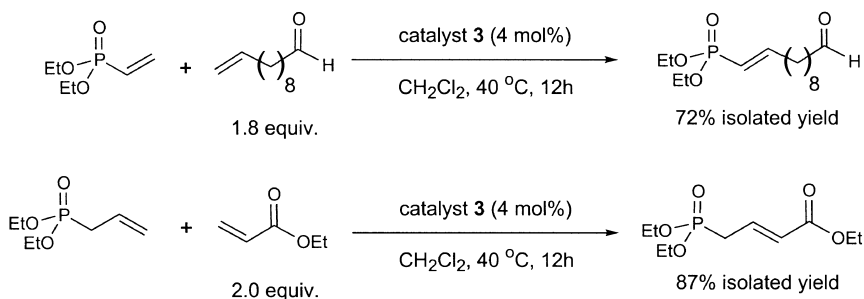
Reagent Synthesis by CM

One of the unique opportunities for CM, when one compares the method to RCM and ROMP, is its ability to provide highly functionalized reagents for further

transformation. This attribute is particularly valuable when a traditional method for the preparation of such reagents is not synthetically straightforward. In addition, because it tolerates a variety of functional groups, one can truly investigate the chemoselectivity of CM, particularly when functional groups are near the reacting olefins. Therefore, demonstrating broad-spectrum chemoselectivity is another area of selectivity that CM must properly address. The following results examine the work done in this area to expand the range of possible CM substrates. One recent example involves the reactions of synthetically versatile δ,γ -unsaturated chromium Fischer carbene complexes with simple α -olefins, to give products with greater than 9:1 *E/Z* ratios, using ruthenium catalysts **2** and **3** [54]. This application is quite remarkable since one transition metal-carbene complex does not interfere with another metal carbene in a given substrate. The following examples indicate how metathesis catalysts can install reactive functional groups into substrates that will then undergo further synthetic manipulations.

For example, the synthesis of unsaturated phosphonates is one possible area in which CM reactions can be exploited in order to produce useful reagents. Olefins that contain phosphonate functionalities are used extensively in synthetic organic chemistry. For example, allylic phosphonates are employed in the preparation of dienes and polyenes by Horner-Emmons olefination. The reaction of organic halides with trialkyl phosphites (Michaelis-Arbuzov reaction) is used primarily for the synthesis of allylphosphonates; however, the palladium-catalyzed cross-coupling of hydrogen phosphonates to conjugated dienes and allenes has also been developed. We have been able to employ catalyst **3** in the CM reactions of vinyl and allylphosphonates using commercially available precursors (Scheme 2.8-26) [55]. For example, compounds with unprotected aldehydes are amenable to the reaction, and the products thereof are appropriately functionalized for a subsequent intramolecular reaction, thereby demonstrating the orthogonality of CM and Horner-Emmons chemistry. Finally, these reactions, as mediated by ruthenium-catalyzed CM, offer a choice of regioselectivity through the judicious selection of CM partners. Palladium-catalyzed hydrophosphorylation, on the other hand, predominantly provides the more substituted 1,1-geminal products.

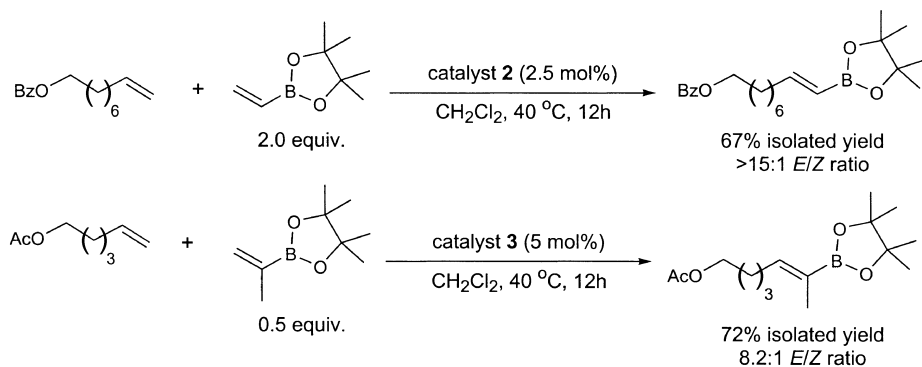
Another area of reagent synthesis impacted by CM methodology involves allylsilane chemistry, and a significant amount of research has been conducted in this



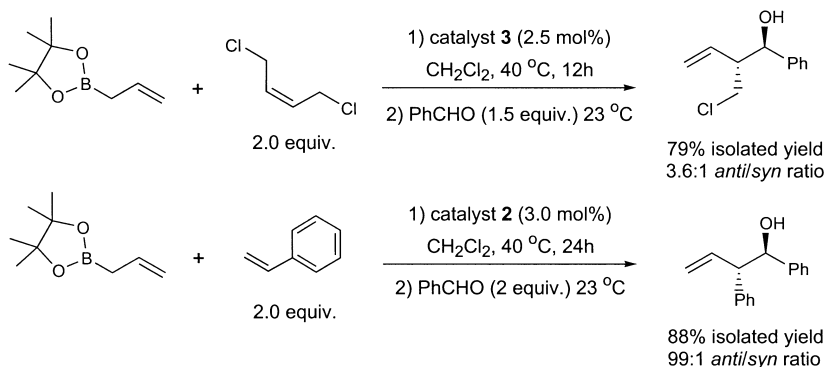
Scheme 2.8-26. CM of unsaturated phosphonates with α -olefins.

area. These products are useful nucleophilic components in carbonyl addition chemistry. Bespalova and coworkers initially looked at commercially available allyltrimethylsilane in simple CM reactions with other terminal olefins in the early 1990s. Their systems relied upon ill-defined tungsten catalysts, however, and no details pertaining to olefin stereoselectivities and product selectivity based on CM partner choices were reported [56]. In addition, Schrock and coworkers reported the dimerization of allyltrimethylsilane with well-defined tungsten carbenes [57]. Several years later, however, Crowe et al. reinvestigated allylsilane CM reactions with molybdenum carbenes and found that they react in a fashion analogous to terminal olefins, as a consequence of the nucleophilic character of these olefins [24]. This feature allows for selective CM reactions to be performed with styrenes and other electrophilic olefins, such as acrylonitriles. When allylsilane CM is performed with α -olefins, statistical product mixtures are achieved in modest 2.6:1 to 4.9:1 *E/Z* ratios. These results provided a rationale for the observed product selectivities based on reactivity patterns of well-defined metal-carbene catalysts. In addition, Blechert and coworkers demonstrated CM with resin-bound allylsilanes, which subsequently underwent protodesilylation [58]. Recently, Cossy and coworkers demonstrated that the CM reaction between allylsilanes and α,β -unsaturated carbonyl compounds proceeds with excellent *trans* stereoselectivity using catalyst 4 [59]. Analogously, CM using catalyst 1 has also resulted in the preparation of 1,2-disubstituted allyl stannanes [60], as ruthenium metathesis catalysts have been found to be inactive with these substrates.

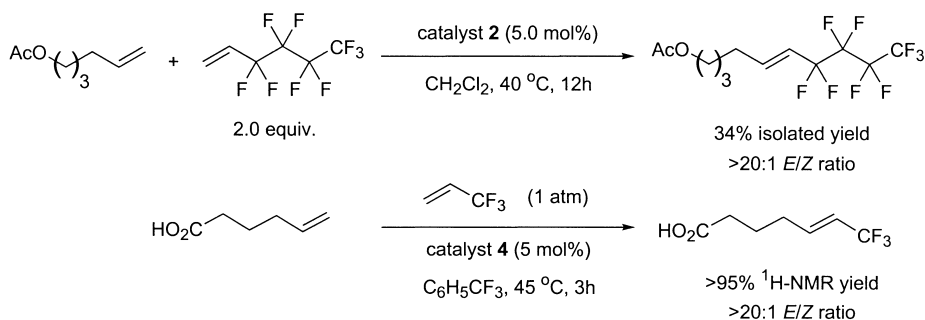
CM has also been used to install other synthetically useful functional groups. For example, vinylboronates participate in CM reactions with α -olefins and proceed with good *E/Z* selectivity. These products are useful for the synthesis of a variety of di- and trisubstituted olefins using Suzuki couplings (Scheme 2.8-27). For the trisubstituted vinylboronate, the CM pathway is advantageous to performing hydroboration of the corresponding alkyne, as a mixture of regioisomers would be obtained from this latter procedure. The regiospecificity of CM is important to note, since the choice of CM partners allows one to access either desired regioisomer. Recently, the concept of reagent synthesis by CM has been appropriately



Scheme 2.8-27. Cross-metathesis of vinylboronates with terminal olefins.



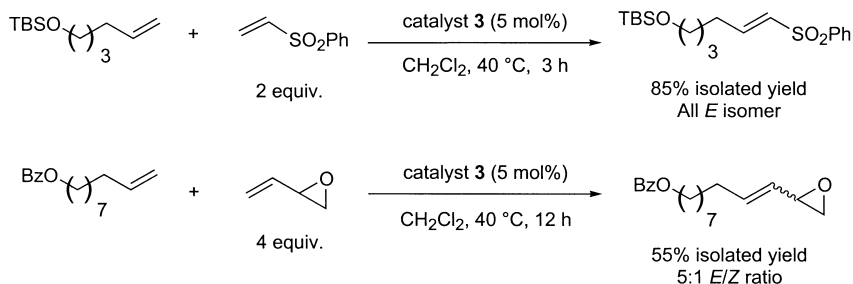
Scheme 2.8-28. One-pot cross-metathesis and allylboration reaction.



Scheme 2.8-29. Cross-metathesis of fluorinated alkane olefins with α -olefins.

extended to allylboronates. These reagents, analogous to allylsilanes discussed previously, have been widely used in highly enantio- and diastereoselective additions to aldehyde and ketone electrophiles. Allylboronates are active for CM with a variety of olefins using catalysts **2** [61] and **3** [62] and can be directly used in subsequent allylation reactions without the need for any purification (Scheme 2.8-28). It was discovered independently that the reaction proceeded best when one foregoes isolation of the 1,2-disubstituted allylboronates before treatment with the desired aldehyde. As seen in these reactions, both catalysts **2** and **3** can furnish good yields of the substituted homoallylic alcohol. It is believed that the *anti/syn* diastereoselectivity is directly related to the *E/Z* ratio obtained from the metathesis reaction. In conclusion, the CM work with unsaturated boronates provides an orthogonal method to traditional organic methods for the synthesis of these highly versatile reagents.

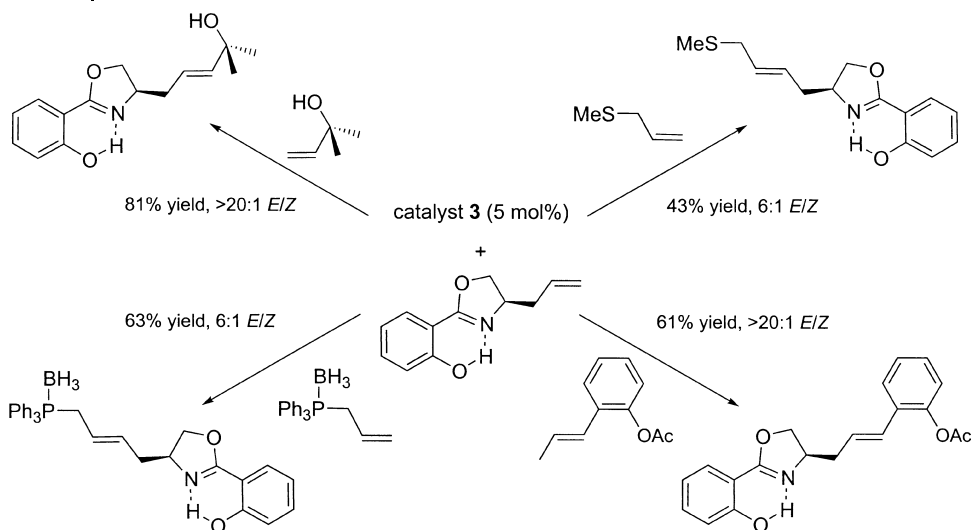
The synthesis of alkenes containing functional groups directly attached to the olefin represents a growing part of CM methodology. Several recent examples have been presented using more active catalyst systems, such as **3** and **5**. Our group disclosed the novel participation of fluoro-alkyl-containing olefins in CM reactions, although the yield was only 34% (Scheme 2.8-29). It should be noted that the bis-phosphine catalyst **2** was unable to provide any product in these reactions. More



Scheme 2.8-30. Vinylsulfone and vinylepoxyde CM using catalyst **3**.

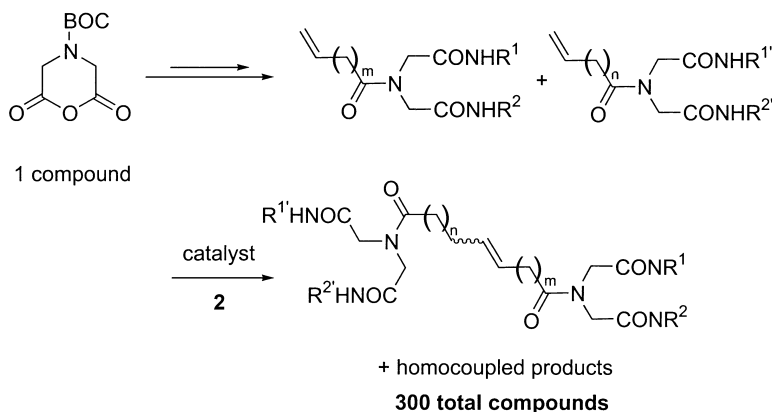
examples of this chemistry have been reported by Blechert and coworkers using catalyst **4** [63]. The homologation of terminal olefins with trifluoropropene is particularly useful and high yielding. The use of fluorinated solvents is novel, and only the *trans* olefin is formed in all these reactions, indicating its synthetic utility. Vinylsulfones and vinylepoxides represent another group of compounds that have been reported to participate in CM reactions mediated by imidazoylidene-containing ruthenium metathesis catalysts (Scheme 2.8-30). Vinylsulfone CM provides yet another example of potential Michael acceptors that can be prepared by metathesis. Brela and Bieniek, using phenyl vinyl sulfones, recently demonstrated highly stereoselective and product-selective CM using catalyst **3** [64]. Interestingly, work in this group showed that methyl vinyl sulfone was not active for CM [45], thereby demonstrating the need to modulate the sulfone substitution patterns for successful CM reactivity, in a manner similar to the allylic substitution effects described previously. In addition, butadiene monoxide participates in cross-metathesis reactions with catalyst **3** in moderate yields [45]. This reaction allows for the simple homologation of olefins with vinyl epoxides, and the products are highly versatile synthons as a consequence of their inherent ring strain. The reactivity of these compounds in CM is unique with catalyst **3**, since catalyst **2** affects only allylic-ether epoxide [25] and homoallylic epoxide [65] CM reactions. In addition, Corey and coworkers had previously reported a vinyl epoxide homodimerization strategy in the synthesis of the squalenoid glabrescol and its *meso* diastereoisomers [66]. One of the remarkable features is the amenability of catalyst **2** toward vinyl epoxide functionality and other substituted olefins in the farnesyl acetate-derived substrate. In summary, these results in vinyl epoxide and vinylsulfone chemistry demonstrate the potential of CM to synthesize highly synthetic intermediates from simple olefinic starting materials.

At this point, concurrent mechanistic work began to provide greater understanding of why imidazoylidene-based catalyst systems **3**–**5** were more active than their parent bis-phosphine catalyst **2**. By detailed mechanistic analysis, it was discovered that the preference for olefin binding in catalyst **3** was over 10,000 times greater (Relative to phosphine) than in catalyst **2** [67]. This fact is particularly interesting because the competing pathway in these systems is rebinding a basic phosphine ligand. In addition, this work also demonstrated that the upper limit to the rate of binding olefin is nearly equivalent to binding phosphine in systems



Scheme 2.8-31. Diversity-oriented ligand synthesis by CM using catalyst **3**.

such as **3**. With this in mind, we decided to investigate the CM reactivity of olefins that also contained potential ligands for ruthenium metal centers. This study is perhaps the true test of functional group tolerance in olefin metathesis, where the catalyst chooses to turn over olefin rather than irreversibly bind a potential ligand. One objective in this chemistry is to make ligands for other metal centers by performing a selective CM with catalyst **3** (Scheme 2.8-31) [68]. For example, reduced oxidation states of sulfur are notoriously good ligands for late transition metal centers as a consequence of soft-soft compatibility, and it was previously demonstrated that sulfides are only tolerated with earlier transition metal catalyst systems, such as **1** [69] and the Basset tungsten system [70]. Shortly after our disclosure of the use of sulfur-containing olefins in RCM and CM protocols, a report by Mioskowski and coworkers reported a larger substrate scope, including the participation of free thiols in CM reactions, in the presence of an unsaturated imidazoylidene version of catalyst **3** [71]. Moreover, sulfides, protected phosphines, and unprotected alcohols were amenable to catalytic CM with catalyst **3** in moderate to good yield and stereoselectivity. These substrates were used in CM reactions with a 2-oxazolyphenol-substituted olefin scaffold, in order to develop a family of novel Salen-based ligands. Salen ligands previously were demonstrated to coordinate to similar ruthenium systems [72] and, in so doing, highlight the remarkable functional group tolerance of catalyst **3**. In conclusion, olefin cross-metathesis methodology is a rapidly growing area of research that provides functionalized products that can be used as substrates for further functional group manipulation. Therefore, by addressing the three main components of selectivity in CM, namely, olefin stereoselectivity, CM product selectivity, and chemoselective CM, a variety of applications of CM reactions have been used in organic synthesis. The discussion of these applications comprises the rest of this chapter.

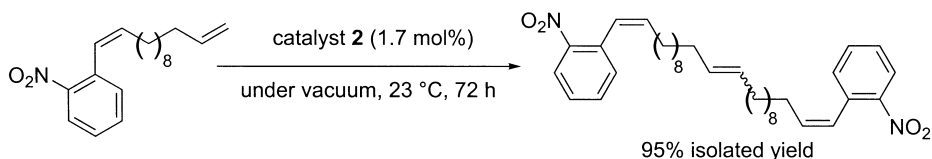


Scheme 2.8-32. Compound library synthesis using CM as a key diversity-introducing element.

2.8.11 Applications of CM

A wide variety of applications of CM reactions have been reported in the literature. In fact, many of the applications of CM predate the development of selective methodology in the area. While much of the work focused on homodimerization reactions, these applications provided the first indications of the significant functional group tolerance exhibited by the single-component metathesis catalysts shown in Figure 2.8-1. Unlike RCM procedures, where total synthesis was the first arena in which single-component metathesis catalysts were first utilized, CM reactions were used primarily in combinatorial, bioorganic, and material chemistry, before it was used in complex total syntheses. This specific evolution of catalyst use can be explained by the initial lack of selective methods available for this approach, rendering chemists wary of subjecting their highly valuable intermediates to CM reactions.

Interestingly, the lack of selectivity in CM protocols led to the initial application of CM in combinatorial chemistry, as a method to introduce structural diversity [73]. For example, Boger and coworkers [74] were able to use solution-phase combinatorial chemistry in generating C_2 -symmetrical and unsymmetrical libraries via CM. In these cases, a variety of tether lengths between two iminodiacetic acid moieties can be introduced, where a statistically controlled CM reaction introduced a high degree of diversity in the library (Scheme 2.8-32). As described above, Blechert et al. investigated the CM reactions of resin bound olefins. With one set of olefins not readily able to undergo homodimerization, however, the reactions had only marginally improved yields [30]. Nonetheless, these reactions did demonstrate that CM could work on resin beads despite a fair amount of site-site cross-reactivity. Interestingly, the phenomenon of solid-phase reactivity has been applied to perform “intra-site” CM reactions to generate homodimers in a rapid fashion via two olefins that reside on the same bead [75]. It is anticipated that more progress will be made in developing efficient processes for the use of CM reactions

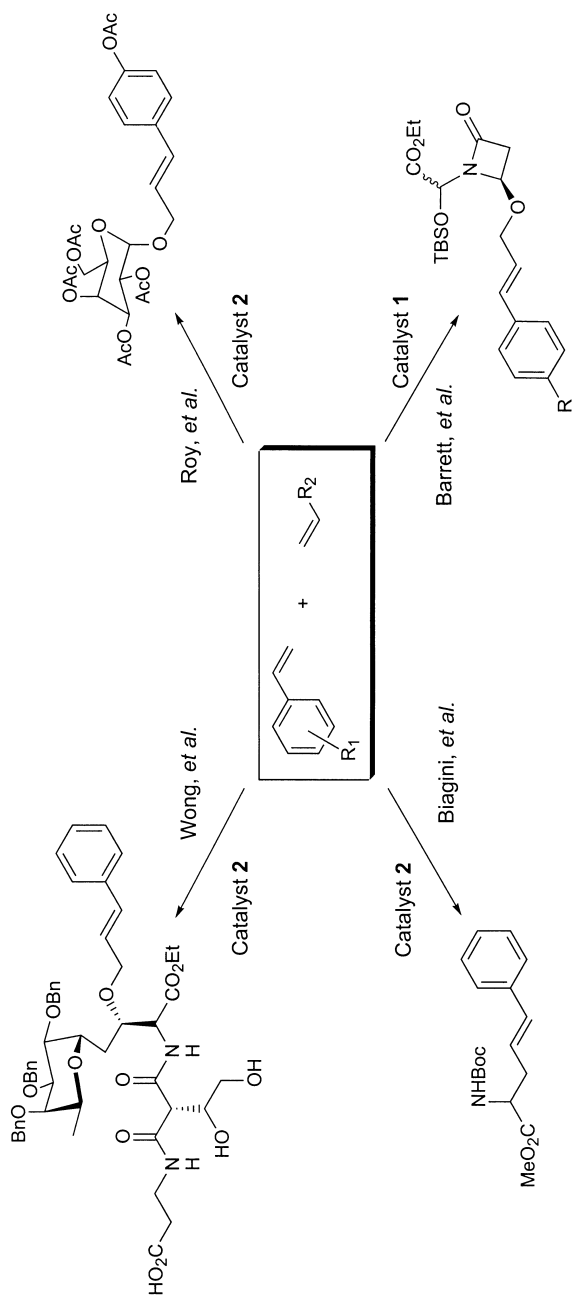


Scheme 2.8-33. Chemoselective CM of a terminal olefin in the presence of a styrene olefin.

in solid-phase syntheses, given the inherent power of CM processes to generate diversity.

While work in developing selective CM methods was still in progress, several groups began applying CM procedures to more functionalized substrates to determine olefin chemoselectivity and functional group tolerance of the well-defined homogeneous catalysts. The application of CM has been demonstrated in several arenas, including materials chemistry, bioorganic chemistry, and, only recently, natural product synthesis. In material science applications, Feher and coworkers demonstrated the homologation of vinyl-substituted silsesquioxanes with a variety of terminal olefins, in moderate to good yields, using catalyst 2 [76]. This report demonstrated one of the earliest applications of CM procedures. These spherically shaped silsesquioxanes have interesting materials properties, and CM allows for rapid access to a diverse set of compounds in one synthetic step simply by changing the CM partners. In very early CM work, Marciniak and coworkers demonstrated selective CM reactions between vinylsiloxanes and a variety of terminal olefins, including styrenes [77]. Additionally, these particular styrene CM reactions provided only the *trans* stereoisomer, thereby making them synthetically useful. The work by Marciniak also demonstrated that another family of directly functionalized olefins, i.e., vinylsiloxanes, can be employed in selective CM reactions. Duran and Kloeppner demonstrated another important application of CM in materials science [78]. These workers demonstrated one of the first olefin chemoselective CM reactions in their synthetic route to polyalkylanilines. These polyalkylanilines were used in the formation of ultrathin Langmuir films for applications in nonlinear optical materials and electroluminescent materials. Using ruthenium-based catalyst 2, terminal olefin dimerization was accomplished cleanly in the presence of a *cis*-styrenyl bond (Scheme 2.8-33). This example demonstrates that olefin chemoselectivity can be accomplished by appropriate catalyst choice. This result is particularly interesting since styrene CM has been widely demonstrated with 2 but can be prevented by the presence of a nitro-withdrawing group, even in a more sterically accessible *cis*-configuration. In addition, the *cis*-styrenyl bond in this example was formed by Wittig chemistry, demonstrating the direct orthogonality between CM and Wittig olefination strategies.

Styrene CM has been widely applied as a consequence of its excellent *trans* selectivity and has been the subject of recent work, as demonstrated above. A summary of some recent examples, mostly directed at bioorganic applications, is outlined in Scheme 2.8-34. These early examples demonstrate the functional group tolerance of metathesis catalysts in CM. Biagini et al. performed styrene CM reactions with protected homoallylglycine derivatives in moderate yields, repre-



Scheme 2.8-34. Early applications of styrene CM in bioorganic chemistry.

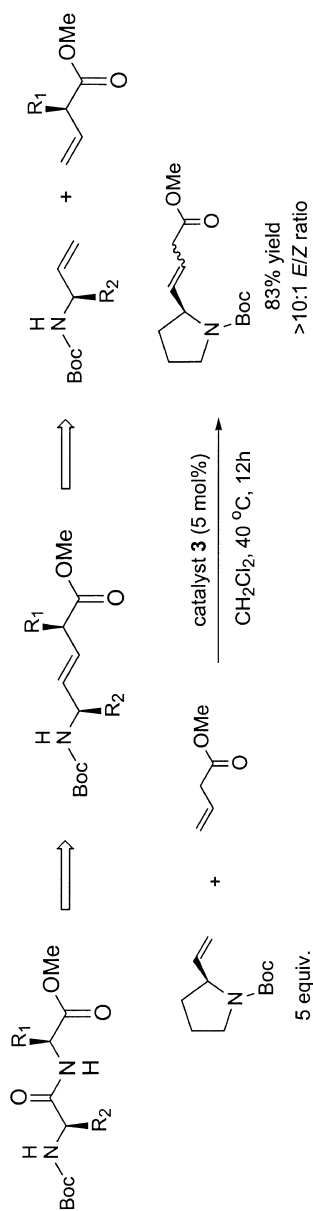
senting some of the early work in CM applications in bioorganic chemistry using catalyst **2** [79]. In other early work, the CM of β -lactams with a variety of *para*-substituted styrenes was reported by Barrett and coworkers using molybdenum catalyst **1** [80]. In addition, Wong and coworkers were able to perform highly efficient styrene CM reactions with **2** in their preparation of Silyl Lewis X mimetics [81]. Roy and coworkers also demonstrated styrene CM reactions with *O*-allyl glycosides to make extended alkenyl glycosides [82]. These last two studies not only illustrate some of the first applications of CM in carbohydrate synthesis but also demonstrate the wide variety of styrenes employable with catalyst **2** to rapidly generate biologically relevant molecules. In fact, these reports establish much of the functional group tolerance now associated with the catalysts in CM procedures and push the limits of CM reactivity with catalyst **2**. This evolution in CM chemistry is quite different from RCM chemistry, since many of applications in RCM were directed toward natural product synthetic endeavors.

2.8.12

Bioorganic Applications of CM

As work in the area of cross-metathesis was being developed, research in the area of application of CM processes to bioorganic systems, in addition to the styrene examples mentioned above, was being performed concurrently. However, much of this work was directed at simple dimerizations rather than performing cross-coupling procedures. Diver and Schreiber reported an important application of CM in the dimerization of immunosuppressant FK506 [83]. The functional group compatibility was a central highlight of this work with the use of ruthenium catalyst **2**, albeit in moderate yields. The lack of protecting groups employed, and the presence of other olefins inert to the reaction conditions, is a remarkable feature of this work and is one of the first chemoselective CM reactions. The use of CM provided a cell-permeable analogue, termed FK1012, which was important in understanding the immunogenic activity of FK506. The groundbreaking work with FK506 homodimerization has also been applied to other natural product dimerizations to further study their biological and medicinal value, including the antibiotic vancomycin [84] and tyrosine kinase inhibitor K-252a [85]. CM reactions may have some further applications in forming biologically stable C–C bonds in order to study a variety of biological targets.

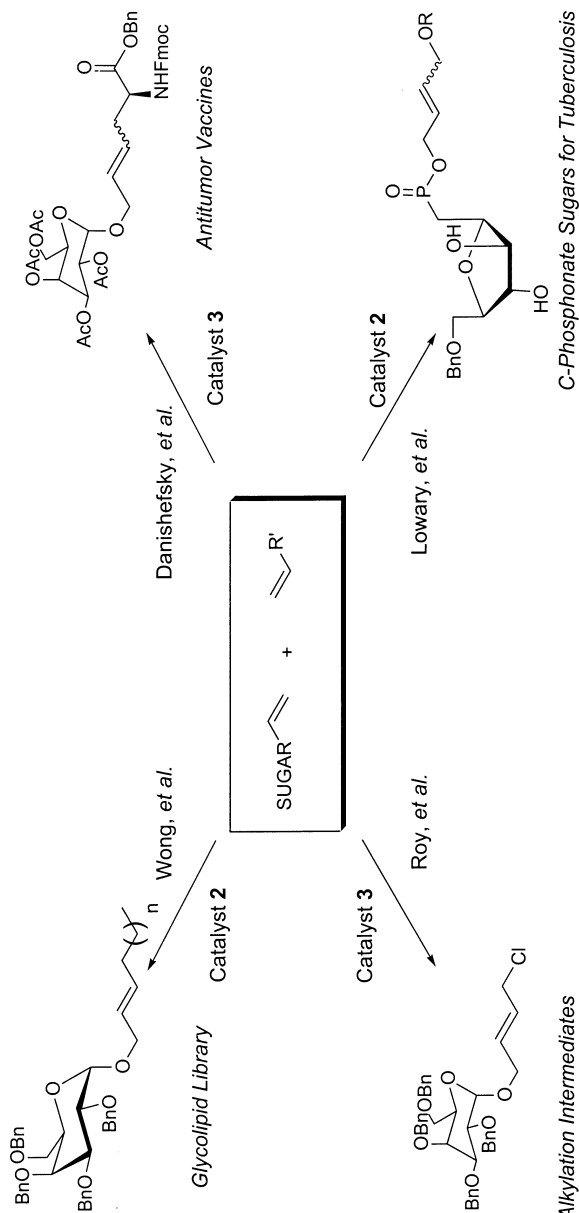
In addition to the use of vinylglycine and allylglycine CM protocols discussed above, several groups have recently investigated the use of CM reactions in the synthesis of novel amino acids and glycosides. A related example in this area, concerned with the synthesis of peptidomimetics, has recently been reported by Vasbinder and Miller [86]. The simple CM reaction between a substituted allylamine and methyl 3-butenolate proceeds with good stereoselectivity and affords moderate yields of CM product (Scheme 2.8-35). Unfortunately, the CM product selectivity is low and requires an excess of the allylamine component; nonetheless, this method does provide a nice example of CM in bioorganic chemistry. In addition, a large



Scheme 2.8-35. Synthesis of peptidomimetics dipeptide isosteres by CM.

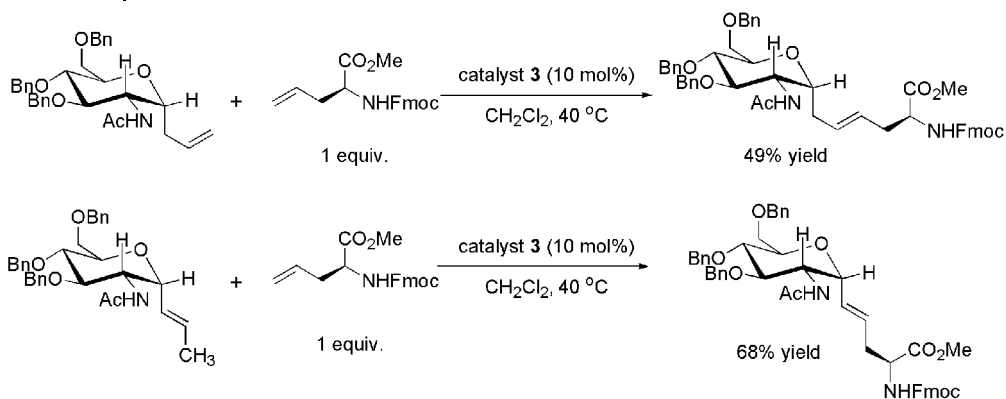
amount of work in glycoside chemistry by several groups has exploited CM methodology in a variety of areas, including early work on glycoside dimerizations [87], synthesis of glycopeptides [88] and glycolipids [89], as well as glycoside CM with allyl halides [90] and allylic alcohols [91]. In addition, arabinofuranose CM has been reported by Centrone and Lowary as a method to generate compounds with anti-tuberculosis activity [92]. All of these examples demonstrate the excellent functional group tolerance of ruthenium-based metathesis catalysts **2** and **3** and demonstrate the broad range of applications of CM in carbohydrate chemistry (Scheme 2.8-36). Perhaps one of the unique applications of CM in carbohydrate chemistry has been in the work of Seeberger and coworkers, with regard to their automated oligosaccharide synthesis protocol [93]. This work demonstrates the unique orthogonality of olefin metathesis with respect to many standard carbohydrate reactions in the context of complex synthesis of up to dodecamer oligosaccharides. As had been exploited earlier in non-carbohydrate systems, Seeberger and coworkers used metathesis in the release of the oligosaccharide from solid support by ethylenolysis, without interruption of the complex carbohydrate functionalities. The area of carbohydrate chemistry has also utilized CM reactions in some recent applications in the synthesis of C-neoglycopeptides [94]. This work provides some important insight into the product selectivity observed in these systems (Scheme 2.8-37). For example, when two terminal olefins are used as the CM partners, a statistical product ratio is obtained. These authors obtained the respective homodimers and found that they were not active for secondary metathesis. However, when the terminal homoallylglycine is converted to a 1,2-disubstituted olefin by an Ir(I) catalyzed olefin isomerization and subsequently used in the CM reaction, a much higher yield (68%) of the CM product is obtained. This increase in product selectivity arises as a consequence of the slower dimerization of the 1,2-disubstituted olefins versus the terminal olefins. These effects may be attributable to subtle differences in the substituted metallocyclobutane intermediates involved in the metathesis pathway. Recently, CM has been demonstrated in the nucleic acid area with the simple dimerization of allylnucleosides of thymidine and uridine bases [95]. In addition, Lear and Hayes reported the cross-metathesis between vinylphosphonate containing nucleotides and vinylnucleosides to generate “dimeric” pyrimidine nucleotides [96]. This work is a significant advance in CM applications to bioorganic chemistry because it is the only example that uses electron-deficient olefins in complex synthesis. Moreover, since the product is obtained only as the *trans* isomer, CM with catalyst **3** offers an advantage in stereoselectivity over Heck olefination. In summary, there is a large number of applications of CM in bioorganic chemistry, and it has provided novel methods for the creation of peptides, nucleotides, and carbohydrates that all contain biologically stable C–C bonds. In the future it is expected that these novel products will allow for a greater understanding of a variety of biological targets.

Although the use of CM in material and biological applications is well established, the utilization of CM by the synthetic organic community has been somewhat more obscure. Until very recently, unlike its intramolecular variant RCM, CM had not been used in a complex target-oriented synthesis. Recent reports in the

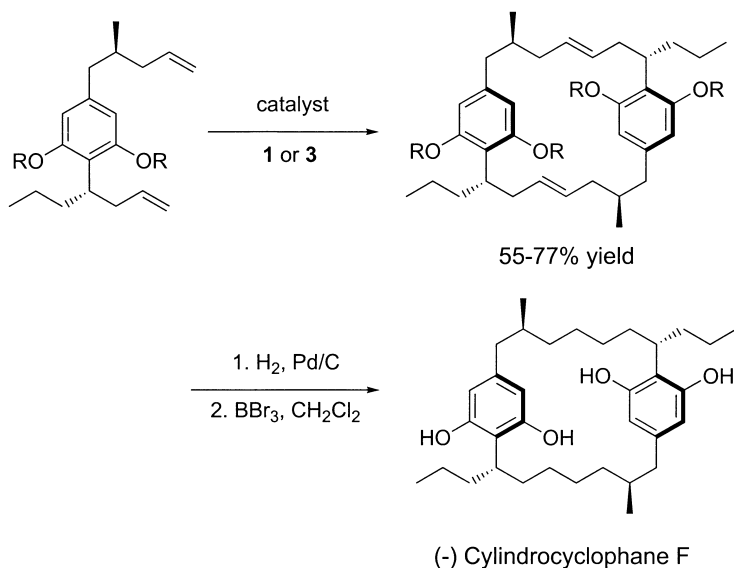


Alkylation Intermediates

Scheme 2.8-36. Cross-metathesis applications in carbohydrate synthesis.



Scheme 2.8-37. Substitution effects on CM efficiency in C-neoglycopeptides synthesis.



Scheme 2.8-38. CM dimerization strategy in cylindrocyclophane synthesis.

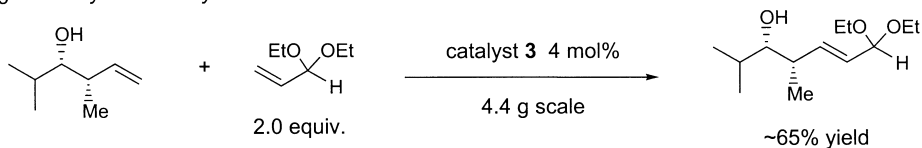
area, however, have focused upon two classes of CM utility, i.e., dimerization strategies and chain extension/elongation. One of the first examples of the dimerization approach was performed by Smith and coworkers in their synthesis of (–)-cylindrocyclophanes A and F (Scheme 2.8-38) [97]. In their synthesis of this class of dimeric natural products, a thermodynamically controlled head-to-tail CM reaction, and subsequent ring-closure, was used to construct a 22-membered cyclophane exclusively as the *E,E*-isomer. Perhaps the most interesting part of this work is the excellent olefin stereocontrol achieved with remote olefinic substitutions in the homoallylic positions. Smith and coworkers also demonstrated that subjecting an independently synthesized head-to-head dimer to the metathesis conditions

lead to the same head-to tail-dimer [7,7]-cyclophane product. The dimerization approaches described to date have highlighted the CM strategy as a functional-group-tolerant method to rapidly generate thermodynamically favored products in excellent yield. In addition, several groups have reported metathesis dimerizations in order to determine the stereochemistry of certain natural products. One example is Corey and Xiong's synthesis of glabrescol diastereomers [66], and another is the report by Nicholas and Molinski with regard to the determination of remote stereochemistry in the dimeric sphingolipid oceanapiside [98]. In a related example, ethylene CM has been used as an alternative to oxidative degradation in the stereochemical determination of (+)-faltarindiol [99].

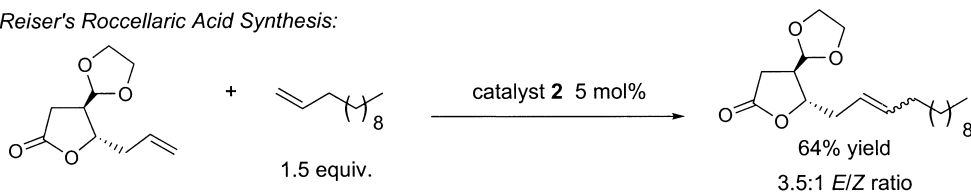
Several examples of chain elongation and derivatization by CM have been recently disclosed, requiring efficient cross-coupling of differing functionalities. Zercher et al., in their formal synthesis of the natural product FR-900848, have demonstrated a chain elongation approach in polycyclopropane synthesis [100]. As previously described in our group, a two-step CM approach was utilized in this synthesis [25]. An initial dimerization of a vinyl cyclopropane substrate provided a homodimer that was subsequently used in excess with another different vinylcyclopropane cross partner to generate the heterocoupled product in excellent yield with moderate stereoselectivity. Interestingly, the CM reaction utilized provided a higher than statistically predicted CM yield, but an explanation for this selectivity was not proffered. In addition, Itoh and coworkers performed CM reactions with fluorinated vinylcyclopropanes and demonstrated that the direct dimerization of certain substituted vinylcyclopropanes proceeds in low yield but does so with exclusive *trans* olefin formation [101]. This example from the target-oriented synthetic literature corroborates independent results, wherein the use of allylic alcohol-protecting groups limits homodimerization and provides enhanced *trans* diastereoselection, as described in Scheme 2.8-6.

Allylic stereocontrol in total synthesis has been well demonstrated by Leighton and coworkers in their synthesis of mycoticin A (Scheme 2.8-39) [102]. As an early step in their formal synthesis effort, they performed acrolein acetal CM reactions

Leighton's Mycoticin A Synthesis:



Reiser's Roccellaric Acid Synthesis:

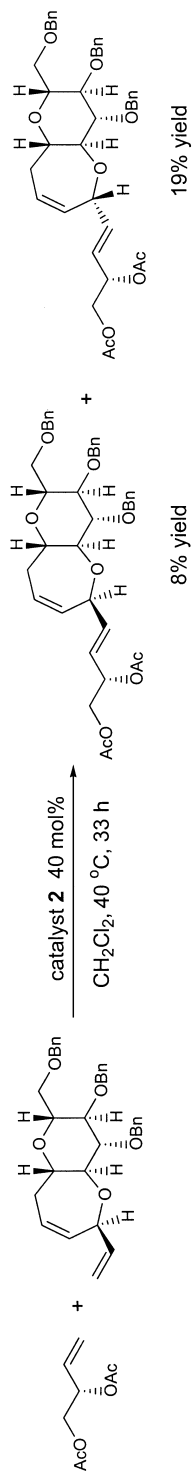


Scheme 2.8-39. Total synthesis applications of terminal olefin homologation by CM.

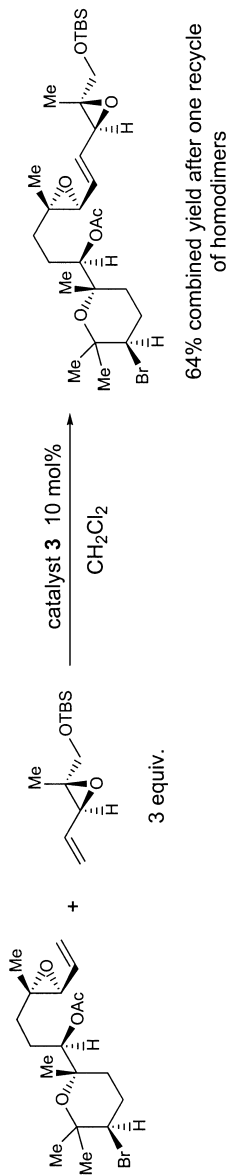
[25] that proceeded with excellent stereocontrol, with substrates possessing both allylic and homoallylic substitution, derived from a crotylation reaction. The imidazoilidene-containing ruthenium catalyst **3** was employed and was demonstrated to be an excellent method for chain elongation with a masked aldehyde source. In the Leighton synthesis, CM was employed early in the synthesis as a consequence of its efficiency in generating a highly functionalized acyclic synthetic precursor. There is also, however, a recent example of a CM reaction that is employed as an endgame in the synthesis. Reiser et al. performed a late-stage CM reaction with 1-dodecene in their synthesis of (–)-roccellaric acid, a member of the γ -butyrolactone family of natural products (Scheme 2.8-39) [103]. By performing a cross-metathesis reaction at the end of the synthesis, a wide variety of side chains can be introduced to generate diversity. This feature of the synthesis is an important factor, as several members of the γ -butyrolactone family of natural products have exhibited antibiotic and antitumor properties, and therefore represents a simple method through which a range of structural analogues can be easily prepared. By analogy, Cossy and coworkers have also used CM in a late-stage chain-elongation reaction in the synthesis of (–)-prosophylline [104] with catalyst **3**, and another late-stage analogue synthesis has been reported in the glycerate portion of the moenomycins [105].

There are two other important examples of functionalized olefin CM procedures in natural product synthesis. First, Hirama and coworkers have demonstrated CM as a route to the AB-ring fragment of ciguatoxin [106]. In their work, a highly convergent CM reaction was performed between a vinyl group and an allylic acetate. The yield is low in this reaction as a consequence of competing ring-opening metathesis of the olefinic cyclic ether. Unfortunately, this reversible ring opening leads to the formation of an undesired diastereoisomer, but this synthesis demonstrates the high degree of convergence in the CM route. McDonald and Wei have used vinyloxy CM to heterocouple two vinyl epoxides in the synthesis of the ABC ring systems of thyriferol and venustatriol [107]. The work by McDonald and Hirama represents two elegant examples of stereoselective CM in natural product synthesis using allylic substitution (Scheme 2.8-40). In addition, the use of α,β -unsaturated carbonyl olefins in total synthesis has been reported by Trost et al. in the synthesis of callipeltoside A and related analogues [108]. An efficient one-pot crotonaldehyde CM reaction with catalyst **3**, and subsequent Takai olefination protocol, is used to introduce novel side chains via a terminal diene iodide. In addition, BouzBouz and Cossy have also used an α,β -unsaturated aldehyde CM reaction in the construction of the C1–C14 fragment of amphidinol **3**, employing an iterative CM and an enantioselective allyltitanation protocol using catalyst **4** [109]. These two previous examples represent the potential utility of combining CM with other stereoselective reactions in a one-pot procedure. In summary, the use of CM protocols by the synthetic organic community in both early and late steps represents the viability of CM to make important bond constructions stereoselectively and in a high yield. CM reactions have also been employed in generating diversity through the use of readily available olefinic cross partners in a highly efficient manner.

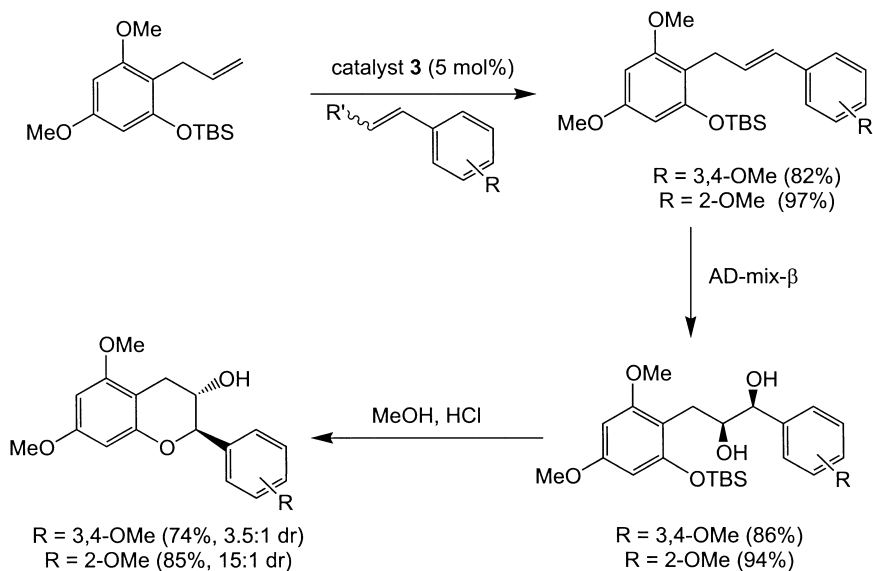
Hirama's AB-ring Synthesis of Ciguatoxin:



McDonald's Tris-THP Synthesis of Thyrseferol and Venustatriol:



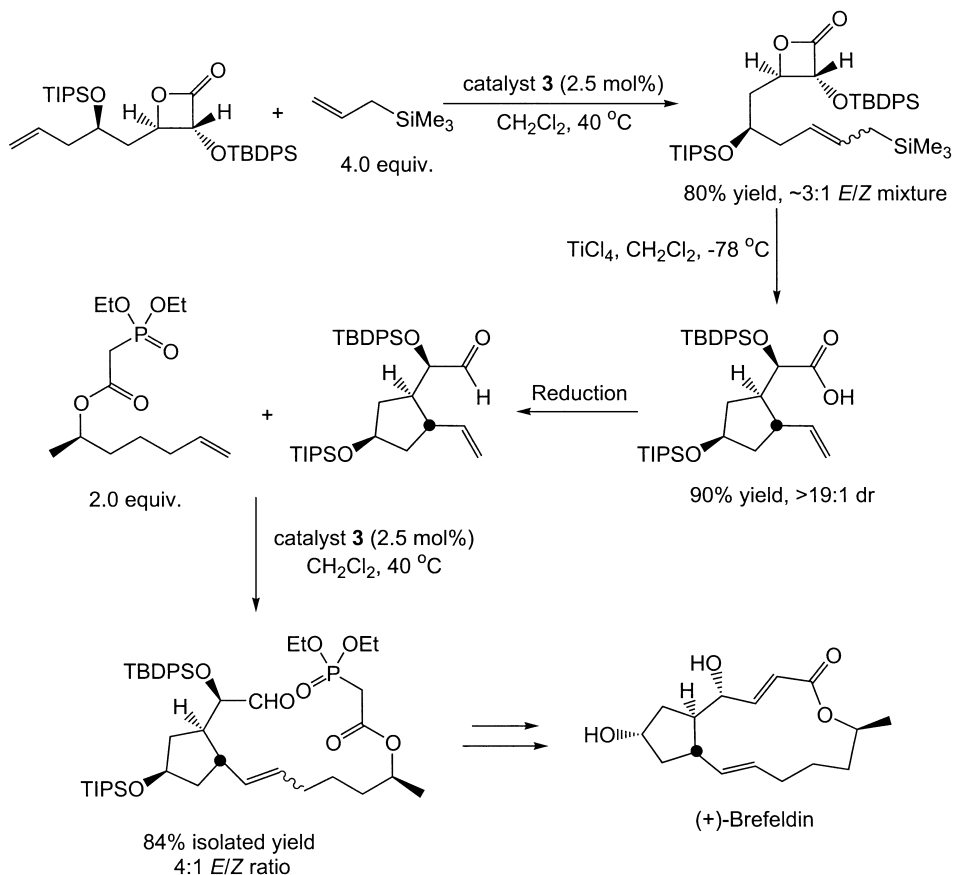
Scheme 2.8-40. Natural product synthesis using allylic functional groups in cross-metathesis.



Scheme 2.8-41. Cross-metathesis route to 3-flavinoids.

There have been two examples where CM has been used to make central carbon-carbon bond constructions in natural product syntheses. First, work from this group [47] and by Gesson and coworkers [110] has demonstrated a route to 3-flavinoids by CM procedures (Scheme 2.8-41). This example is unique in that it uses the stereoselective olefin formed from a CM reaction in a subsequent stereoselective dihydroxylation reaction to install the central C–C bonds and C–heteroatom bonds in the natural product. This approach is in contrast to several of the previous examples where the olefin is retained in the natural product (e.g., mycoticin A, garsubellin A, and callipeltoside A) or is simply hydrogenated away, such as in (–)-roccellaric acid and (–)-prosophylline. It is anticipated that selective CM reactions will be coupled with other stereoselective reactions in an effort to synthesize complex molecules in a highly efficient manner.

Another important example of utilizing a CM strategy as a central bond-constructing method is in synthesis of (+)-brefeldin by Wang and Romo [111]. These workers have recently applied vinylcyclopentane CM, originally described by this group [25], in the synthesis of (+)-brefeldin. They were able to use two CM reactions in their synthetic route, demonstrating one of the first examples of CM as a key step in total synthesis. In an early step in their synthesis, they were able to install an allylsilane moiety by CM, followed by addition into the β -lactone, to provide a highly diastereoselective synthesis of the vinylcyclopentane core (Scheme 2.8-42). An additional CM reaction was used in an extremely convergent manner to install one of the two olefins in the natural product. The CM partner was used in twofold excess, but it provided a higher yield of CM product than the expected statistical distribution. Although the stereoselectivity in the cross-metathesis is moderate (4:1 *E/Z*), the convergent nature of the synthesis, and the mild reaction



Scheme 2.8-42. Selective CM reactions as central C–C bond formation in (+)-brefeldin synthesis.

conditions of the CM step, provides a nice application of the vinylcyclopentane CM methodology. The authors also noted that the dimerization of the substituted vinylcyclopentane is slower and illustrates that subtle steric differences can increase CM reaction efficiency. Once more, this example exemplifies the excellent functional group orthogonality between olefin CM reactions and Horner-Wadsworth-Emmons olefination procedures. Finally, even though we demonstrated that catalyst **2** could employ vinylcyclopentane as the CM partner, these authors required the use of the more active catalyst **3** to afford useful yields of the CM product. These examples suggest that olefin cross-metathesis will eventually find greater application in total synthesis and that the early work done in bioorganic applications is responsible for setting the foundations of this methodology. Coupled with the development of more selective CM methodology, it is believed that this reaction will be as widely, if not more widely, used in organic synthesis than both RCM and ROMP procedures.

2.8.13

CM Product-Selectivity Model

As discussed above, there has been a growing number of selective CM processes reported in the literature, including their application to complex organic synthesis. For further applications of CM in organic synthesis, it would be useful to organize and highlight product-selective CM reactions in a straightforward manner; a model developed by the Caltech group is described below. A comprehensive product-selectivity model is particularly valuable given the various possible alkylidene intermediates and the numerous primary and secondary metathesis pathways involved in a cross-metathesis reaction. The most convenient way to rank olefin reactivity is to examine its ability to homodimerize. Rather than simply looking at *absolute* homodimerization as a measure of an olefin's ability to participate in selective CM reactions, *relative* homodimerization best describes the propensity of olefins to undergo homodimerization reactions. This analysis leads to a general model that comprises four distinct olefin types that can be used to predict both selective and non-selective CM reactions (Figure 2.8-2) [112]. By performing reactions with olefins that lead to selective CM, one can overcome the issue of statistical product distributions presented in Scheme 2.8-3.

Type I olefins are categorized as those that are able to undergo a rapid homodimerization and whose homodimers can equally participate in CM. Type II olefins homodimerize slowly, and, unlike Type I olefins, their homodimers can be consumed only with difficulty in subsequent metathesis reactions. Type III olefins are essentially unable to undergo homodimerization in the presence of the catalyst but are still able to participate in CM reactions with type I and type II olefins. Type IV olefins are not affected by a particular catalyst but do not inhibit catalyst activity toward other olefins. Outside of these categories are olefins that deactivate the catalyst. The desire to use these olefins, as well as type IV olefins, continues to drive the development of more active and functional-group tolerant catalysts. After a survey of the literature and the CM reactions described for catalysts 1–3 above, olefins can be placed into their appropriate category, as shown in Figure 2.8-3. This

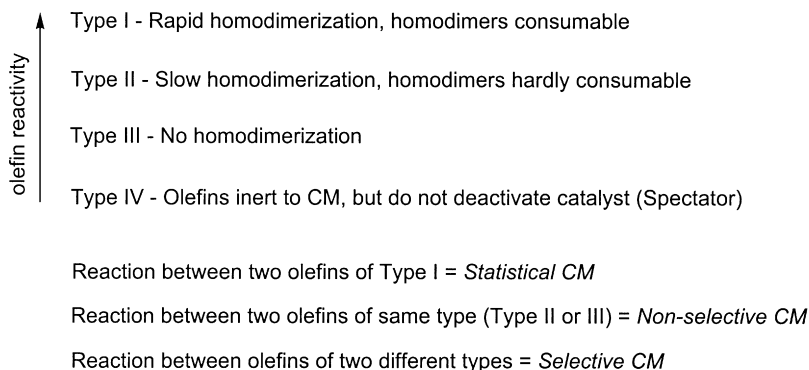


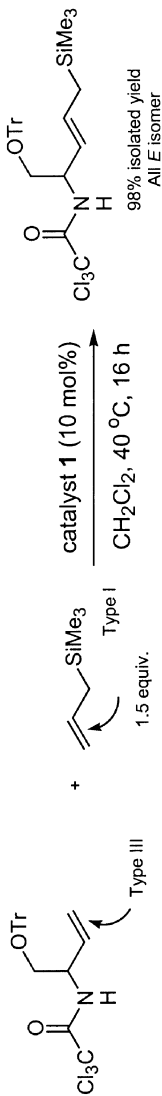
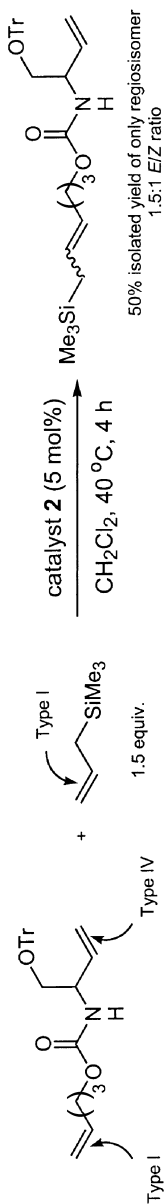
Fig. 2.8-2. Olefin categorization and rules for selective CM.

model can predict where product selectivity can be achieved and is represented in Scheme 2.8-43. For example, Blechert et al. used steric constraints and heteroatom functionality to demonstrate that a highly substituted allylamine (type IV for catalyst 2) could be benign to CM reactions in the presence of two type I olefins. Interestingly, in the same report by Blechert, catalyst 1 was used to effect a highly selective CM reaction of that protected allylamine (type III for catalyst 1) with allylsilanes (type I) in excellent yield and product selectivity [27]. Similarly, Crowe and Zhang performed a successful selective CM between a type I terminal olefin and styrene (type II for catalyst 1) in the presence of a 1,1-disubstituted olefin (type IV) [34]. As demonstrated previously in Scheme 2.8-16, with the more active catalyst 3, 1,1-disubstituted olefins are a type III olefin and, as such, are active for CM to form trisubstituted olefins. This feature reveals that while more active catalysts will have a larger set of CM-active olefins (type I, II, III), it is still very useful to understand which substrates are type IV olefins for less active catalysts in an effort to help determine possible chemoselective CM reactions. While electronic and steric parameters associated with olefins are key contributing factors to the way in which olefins are classified, other factors are often considered in determining selectivity, including chelating ability of certain functional groups to metal catalysts. For example, the effects of carbonyl groups, such as acetate-protecting groups, and allylic heteroatoms have been observed to alter reactivity in CM. It is for these reasons that a comprehensive empirical model is necessary that accounts for all of these observations made about all of the methodology that exists in CM protocols with different catalysts. This model will assist the further application of product-selective CM reactions in target-oriented synthesis.

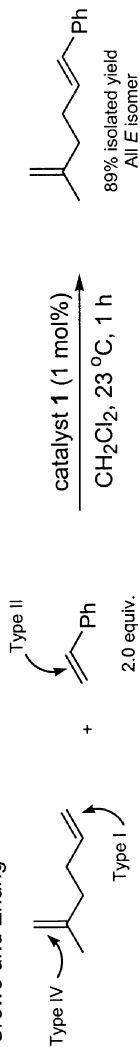
2.8.14

Conclusions

In conclusion, the use of olefin cross-metathesis has begun to garner attention as a viable tool in organic synthesis. Many fundamental studies on functional group tolerance, electronic factors, and steric parameters required for stereoselective synthesis have been investigated with a variety of catalyst systems. In fact, some of the most exciting work is related to the selective CM product formation that is achieved by slowing the homodimerization of one olefin partner. Simultaneously, CM methodology has been applied to total synthesis and to challenges in the biological chemistry area in order to generate rigid alkenyl C–C bond constructions. In fact, the central challenges in CM still center on eliminating homocoupling products, generating products with good stereoselectivity, and increasing substrate scope. In addition, extensive organometallic studies to improve overall catalyst activity will allow for reactions to proceed with lower catalyst loadings, resulting in the efficient preparation of bulk starting materials. This opportunity reflects challenges unique to CM processes as compared to those in endgame RCM and ROMP applications. The ability to appreciate the contributions made in reported CM



Work by Crowe and Zhang



Scheme 2.8-43. Selective CM model in literature using catalysts **1** and **2**.

approaches, as summarized in Figure 2.8-3, will provide even greater applications for olefin metathesis in organic synthesis.

References

- 1 SHARPLESS, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.
- 2 For recent work on sequential Pd-catalyzed reactions to highly substituted olefins, see: ITAMI, K.; NOKAMI, T.; ISHIMURA, Y.; MITSUDO, K.; KAMEI, T.; YOSHIDA, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577.
- 3 For a summary of Heck reactions in fine chemical productions, see: DE VRIES, J. G. *Can. J. Chem.* **2001**, *79*, 1086.
- 4 (a) TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) HERRMANN, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1291.
- 5 (a) PIOTTI, M. E. *Curr. Opin. Solid St. M.* **1999**, *4*, 539; (b) HILLMYER, M. A. *Curr. Opin. Solid St. M.* **1999**, *4*, 559; (c) FEAST, W. J.; KHOSRAVI, E. *J. Fluor. Chem.* **1999**, *100*, 117.
- 6 FÜRSTNER, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3013; (c) KOTHA, S.; SREENIVASA-SACHARY, N. *Ind. J. Chem. B*, **2001**, *40*, 763.
- 7 IVIN, K. V.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, London, 1997.
- 8 Representative examples of Suzuki chemistry, include: (a) ORGAN, M. G.; BILOKIN, Y. V.; BRATOVANOV, S. *J. Org. Chem.* **2002**, *67*, 5176; (b) SCHEIDT, K. A.; BANNISTER, T. D.; TASAKA, A.; WENDT, M. D.; SAVALL, B. M.; FEGLEY, G. J.; ROUSH, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981; (c) ROUSH, W. R.; SCIOTTI, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.
- 9 For some recent reports in Stille chemistry, see: (a) PATTENDEN, G.; SINCLAIR, D. J. *J. Organomet. Chem.* **2002**, *653*, 261; (b) USUDA, H.; KANAI, M.; SHIBASAKI, M. *Tetrahedron Lett.* **2002**, *43*, 3621; (c) PAQUETTE, L. A.; DUAN, M. S.; KONETZKI, I.; KEMPMANN, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 4257.
- 10 For a few recent report of Heck chemistry in synthesis, see: (a) GUILLON, C.; BEUNARD, J. L.; GRAS, E.; THAL, C. *Angew. Chem. Int. Ed.* **2001**, *40*, 4745.
- 11 (a) SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DIMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875; (b) BAZAN, G. C.; KHOSRAVI, E.; SCHROCK, R. R.; FEAST, W. J.; GIBSON, V. C.; O'REGAN, M. B.; THOMAS, J. K.; DAVIS, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378; (c) BAZAN, G. C.; OSKAM, J. H.; CHO, H. N.; PARK, L. Y.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.
- 12 (a) SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem.* **1995**, *107*, 2179; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039; (b) SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100; (c) BELDERRAIN, T. R.; GRUBBS, R. H. *Organometallics* **1997**, *16*, 4001.
- 13 (a) SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953; (b) SANFORD, M. S.; LOVE, J. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
- 14 (a) FÜRSTNER, A.; GUTH, O.; DÜFFELS, A.; SEIDEL, G.; LIEBL, M.; GABOR, B.; MYNOTT, R. *Chem.-Eur. J.* **2001**, *7*, 4811; (b) GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168; (c) WAKAMATSU, H.; BLECHERT, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2403.
- 15 Recent RCM examples include: (a) FÜRSTNER, A.; RADKOWSKI, K.; WIRTZ, C.; GODDARD, R.; LEHMANN, C. W.; MYNOTT, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061; (b) SUN, J.; SINHA, S. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1381.
- 16 For an interesting biological application, see: GESTWICKI, J. E.; STRONG, L. E.; CAIRO, C. W.; BOEHM, F. J.; KIESSLING, L. L. *Chem. & Biol.* **2002**, *9*, 163, and references therein.

- 17 LEHMAN, S. E.; WAGENER, K. B. *Macromolecules* **2002**, 35, 48.
- 18 LA, D. S.; SATTELY, E. S.; FORD, J. G.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2001**, 123, 7767.
- 19 (a) SEIDERS, T. J.; WARD, D. W.; GRUBBS, R. H. *Org. Lett.* **2001**, 3, 3225; (b) DOLMAN, S. J.; SATTELY, E. S.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **2002**, 124, 6991.
- 20 LA, D. S.; SATTELY, E. S.; FORD, J. G.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2001**, 123, 7767.
- 21 For an excellent comparison of catalyst activity on olefin scrambling by CM, see: MOL, J. C. *Green Chem.* **2002**, 4, 5.
- 22 AHMED, M.; ARNAULD, T.; BARRETT, A. G. M.; BRADDOCK, D. C.; FLACK, K.; PROCOPIOU, P. A. *Org. Lett.* **2000**, 2, 551.
- 23 (a) FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, 114, 5426; (b) EVANS, P. A.; MURTHY, V. S. J. *Org. Chem.* **1998**, 63, 6768; (c) DENMARK, S. E.; YANG, S.-M. *Org. Lett.* **2001**, 3, 1749.
- 24 CROWE, W. E.; GOLDBERG, D. R.; ZHANG, Z. J. *Tetrahedron Lett.* **1996**, 37, 2117.
- 25 BLACKWELL, H. E.; O'LEARY, D. J.; CHATTERJEE, A. K.; WASHENFELDER, R. A.; BUSSMANN, D. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, 122, 58.
- 26 MAISHAL, T. K.; SINHA-MAHAPATRA, D. K.; PARANJAPPE, K.; SARKAR, A. *Tetrahedron Lett.* **2002**, 43, 2263.
- 27 BRÜMMER, O.; RÜCKERT, A.; BLECHERT, S. *Chem. Eur. J.* **1997**, 3, 441.
- 28 ENGELHARDT, F. C.; SCHMITT, M. J.; TAYLOR, R. E. *Org. Lett.* **2001**, 3, 2209.
- 29 CHATTERJEE, A. K.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2002**, 41, 3171.
- 30 SCHUSTER, M.; PERNERSTORFER, J.; BLECHERT, S. *Angew. Chem.* **1996**, 108, 2111; *Angew. Chem. Int. Ed.* **1996**, 35, 1979.
- 31 TANG, Q.; WAREING, J. R. *Tetrahedron Lett.* **2001**, 42, 1399.
- 32 WARWEL, S.; WINKELMULLER, W. *J. Mol. Cat.* **1985**, 28, 247.
- 33 FOX, H. H.; SCHROCK, R. R.; O'DELL, R. *Organometallics* **1994**, 13, 635.
- 34 CROWE, W. E.; ZHANG, Z. J. *J. Am. Chem. Soc.* **1993**, 115, 10998.
- 35 BANASIAK, D. S. *J. Mol. Cat.* **1985**, 28, 107.
- 36 ULMAN, M.; GRUBBS, R. H. *Organometallics* **1998**, 17, 2484.
- 37 KONZELMAN, J.; WAGENER, K. B. *Macromolecules* **1995**, 28, 4686.
- 38 CHATTERJEE, A. K.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 1751.
- 39 CHATTERJEE, A. K.; SANDERS, D. P.; GRUBBS, R. H. *Org. Lett.* **2002**, 4, 1939.
- 40 SPESSARD, S. J.; STOLTZ, B. M. *Org. Lett.* **2002**, 4, 1943.
- 41 WIPF, P.; RECTOR, S. R.; TAKAHASHI, H. *J. Am. Chem. Soc.* **2002**, 124, 14848.
- 42 CROWE, W. E.; GOLDBERG, D. R. *J. Am. Chem. Soc.* **1995**, 117, 5162.
- 43 COSSY, J.; BOUZBOUZ, S.; HOVEYDA, A. H. *J. Organomet. Chem.* **2001**, 624, 327.
- 44 SESHADRI, H.; LOVELY, C. J. *Org. Lett.* **2000**, 2, 327.
- 45 CHATTERJEE, A. K.; MORGAN, J. P.; SCHOLL, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, 122, 3783.
- 46 CHOI, T.-L.; CHATTERJEE, A. K.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2000**, 39, 1277.
- 47 CHATTERJEE, A. K.; TOSTE, F. D.; CHOI, T.-L.; GRUBBS, R. H. *Adv. Synth. Catal.* **2002**, 344, 634.
- 48 SUGIONO, E.; DETERT, H. *Synthesis* **2001**, 893.
- 49 (a) YASUDA, T.; ABE, J.; IYODA, T.; KAWAI, T. *Chem. Lett.* **2001**, 812; (b) YASUDA, T.; ABE, J.; YOSHIDA, H.; IYODA, T.; KAWAI, T. *Adv. Synth. Catal.* **2002**, 344, 705.
- 50 RANDL, S.; GESSLER, H.; WAKAMATSU, H.; BLECHERT, S. *Chem. Commun.* **2002**, 1148.
- 51 LOVE, S. A.; MORGAN, J. P.; TRNKA, T. M.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2002**, 41, 4035.
- 52 SCHUSTER, M.; BLECHERT, S. *Angew. Chem.* **1997**, 109, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2036.
- 53 CHOI, T.-L.; LEE, C. W.; CHATTERJEE, A. K.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, 123, 10417.
- 54 ZHANG, L.; HERNDON, J. W. *Tetrahedron Lett.* **2002**, 43, 4471.
- 55 CHATTERJEE, A. K.; CHOI, T.-L.; GRUBBS, R. H. *Synlett* **2001**, 1034.
- 56 BESPALOVA, N. B.; BOVINA, M. A. *J. Mol. Cat.* **1992**, 76, 181.

- 57 SCHAEVERIEN, C. J.; DEWAN, J. C.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 2771.
- 58 SCHUSTER, M.; LUCAS, N.; BLECHERT, S. *Chem. Commun.* **1997**, 823.
- 59 BOUZBOUZ, S.; DE LEMOS, E.; COSSY, J. *Adv. Synth. Catal.* **2002**, *344*, 627.
- 60 FENG, J.; SCHUSTER, M.; BLECHERT, S. *Synlett* **1997**, 129.
- 61 YAMAMOTO, Y.; TAKAHASHI, M.; MIYAURA, N. *Synlett* **2002**, 128.
- 62 GOLDBERG, S. D.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 807.
- 63 IMHOF, S.; RANDL, S.; BLECHERT, S. *Chem. Commun.* **2002**, 1692.
- 64 GRELA, K.; BIENIEK, M. *Tetrahedron Lett.* **2001**, *42*, 6425.
- 65 LANGER, P.; HOLTZ, E. *Synlett* **2002**, 110.
- 66 XIONG, Z.; COREY, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831.
- 67 SANFORD, M. S.; ULMAN, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.
- 68 TOSTE, F. D.; CHATTERJEE, A. K.; GRUBBS, R. H. *Pure Appl. Chem.* **2002**, *74*, 7.
- 69 SHON, Y.-S.; LEE, T. R. *Tetrahedron Lett.* **1997**, *38*, 1283.
- 70 COUTURIER, J.-L.; TANAKA, K.; LECONTE, M.; BASSET, J.-M.; OLLIVIER, J. *Angew. Chem.* **1993**, *105*, 99; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 112.
- 71 SPAGNOL, G.; HECK, M.-P.; NOLAN, S. P.; MIOSKOWSKI, C. *Org. Lett.* **2002**, *4*, 1767.
- 72 CHANG, S.; JONES II, L.; WANG, C.; HENLING, L. M.; GRUBBS, R. H. *Organometallics* **1998**, *17*, 3460.
- 73 BRÄNDLI, C.; WARD, T. R. *Helv. Chim. Acta* **1998**, *81*, 1616.
- 74 (a) BOGER, D. L.; CHAI, W.; OZER, R. S.; ANDERSSON, C.-M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 463. (b) BOGER, D. L.; CHAI, W. *Tetrahedron* **1998**, *54*, 3955.
- 75 (a) CONDE-FRIEBOES, K.; ANDERSEN, S.; BREINHOLT, J. *Tetrahedron Lett.* **2000**, *41*, 9153; (b) BLACKWELL, H. E.; CLEMONS, P. A.; SCHREIBER, S. L. *Org. Lett.* **2001**, *3*, 1185.
- 76 FEHER, F. J.; SOULIVONG, D.; EKLUND, A. G.; WYNDHAM, K. D. *Chem. Commun.* **1997**, 1185.
- 77 PIETRASZUK, C.; FISCHER, H.; KUJAWA, M.; MARCINIEC, B. *Tetrahedron Lett.* **2001**, *42*, 1175, and references therein.
- 78 KLOEPPNER, L. J.; DURAN, R. S. *J. Am. Chem. Soc.* **1999**, *121*, 8108.
- 79 (a) GIBSON, S. E.; GIBSON, V. C.; KEEN, S. P. *Chem. Commun.* **1997**, 1107; (b) BIAGINI, S. C. G.; GIBSON, S. E.; KEEN, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485.
- 80 (a) BARRETT, A. G. M.; BAUGH, S. P. D.; GIBSON, V. C.; GILES, M. R.; MARSHALL, E. L.; PROCOPIOU, P. A. *Chem. Commun.* **1996**, 2231; (b) BARRETT, A. G. M.; BAUGH, S. P. D.; GIBSON, V. C.; GILES, M. R.; MARSHALL, E. L.; PROCOPIOU, P. A. *Chem. Commun.* **1997**, 155.
- 81 HUWE, C. M.; WOLTERING, T. J.; JIRICEK, J.; WEITZ-SCHMIDT, G.; WONG, C.-H. *Bioorg. Med. Chem.* **1999**, *773*.
- 82 ROY, R.; DOMINIQUE, R.; DAS, S. K. *J. Org. Chem.* **1999**, *64*, 5408.
- 83 DIVER, S. T.; SCHREIBER, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 5106.
- 84 NICHOLAOU, K. C.; HUGHES, R.; CHO, S. K.; WINSSINGER, N.; LABISCHINSKI, H.; ENDERMANN, R. *Chem. Eur. J.* **2001**, *7*, 3824.
- 85 TAMAKI, K.; HUNTSMAN, E. W. D.; PETSCH, D. T.; WOOD, J. L. *Tetrahedron Lett.* **2002**, *43*, 379.
- 86 VASBINDER, M. M.; MILLER, S. J. *J. Org. Chem.* **2002**, *67*, 6240.
- 87 (a) DOMINIQUE, R.; DAS, S. K.; ROY, R. *Chem. Commun.* **1998**, 2437; (b) KIRSCHNING, A.; CHEN, G. *Tetrahedron Lett.* **1999**, *40*, 4665; (c) GAN, Z.; ROY, R. *Tetrahedron* **2000**, *56*, 1423; (d) LIN, C.-C.; SUBRAMANIAN, T.; HUS, T.-S.; FAN, G.-T.; LIN, C.-C. *J. Chin. Chem. Soc.* **2001**, *48*, 55; (e) DOMINIQUE, R.; ROY, R. *Tetrahedron Lett.* **2002**, *43*, 395; (f) LIU, B.; ROY, R. *Chem. Commun.* **2002**, 594; (g) CHEN, G.; KIRSCHNING, A. *Chem. Eur. J.* **2002**, *8*, 2717.
- 88 (a) HU, Y.-H.; ROY, R. *Tetrahedron Lett.* **1999**, *40*, 3305; (b) BISWAS, K.; COLTART, D. M.; DANISHEFSKY, S. J. *Tetrahedron Lett.* **2002**, *43*, 6107; (c) DONDONI, A.; GIOVANNINI, P. P.; MARRA, A. J. *Chem. Soc., Perkin Trans. 1* **2001**, 2380.

- 89 (a) EL SUKKARI, H.; GESSON, J.-P.; RENOUX, B. *Tetrahedron Lett.* **1998**, 39, 4043; (b) PLETTENBURG, O.; MUI, C.; BODMER-NARKEVITCH, V.; WONG, C.-H. *Adv. Synth. Catal.* **2002**, 344, 622.
- 90 LIU, B.; DAS, S. K.; ROY, R. *Org. Lett.* **2002**, 4, 2723.
- 91 POSTEMA, M. H. D.; PIPER, J. L. *Tetrahedron Lett.* **2002**, 43, 7095.
- 92 CENTRONE, C. A.; LOWARY, T. L. *J. Org. Chem.* **2002**, 67, 8862.
- 93 PLANTE, O. J.; PALMACCI, E.; SEEBERGER, P. H. *Science* **2001**, 291, 1523.
- 94 MCGARVEY, G. J.; BENEDUM, T. E.; SCHMIDTMANN, F. W. *Org. Lett.* **2002**, ASAP article.
- 95 BATOUX, N.; BENHADDOU-ZERROUKI, R.; BRESSOLIER, P.; GRANET, R.; LAUMONT, G.; AUBERTIN, A.-M.; KRAUSZ, P. *Tetrahedron Lett.* **2001**, 42, 1491.
- 96 LERA, M.; HAYES, C. J. *Org. Lett.* **2001**, 3, 2765.
- 97 SMITH, A. B.; ADAMS, C. M.; KOZMIN, S. A.; PAONE, D. V. *J. Am. Chem. Soc.* **2001**, 123, 5925.
- 98 NICHOLAS, G. M.; MOLINSKI, T. F. *J. Am. Chem. Soc.* **2000**, 122, 4011.
- 99 RATNAYAKE, A. S.; HEMSCHIEDT, T. *Org. Lett.* **2002**, 4, 4667.
- 100 VERBICKY, C. A.; ZERCHER, C. K. *Tetrahedron Lett.* **2000**, 41, 8723.
- 101 ITOH, T.; MITSUKURA, K.; ISHIDA, N.; UNEYAMA, K. *Org. Lett.* **2000**, 2, 1431.
- 102 DREHER, S. D.; LEIGHTON, J. L. *J. Am. Chem. Soc.* **2001**, 123, 341.
- 103 BOHM, C.; REISER, O. *Org. Lett.* **2001**, 3, 1315.
- 104 (a) COSSY, J.; WILLIS, C.; BELLOSTA, V. *Synlett* **2001**, 1578; (b) COSSY, J.; WILLIS, C.; BELLOSTA, V.; BOUZBOUZ, S. *J. Org. Chem.* **2002**, 67, 1982.
- 105 EICHELBERGER, U.; MANSOUROVA, M.; HENNIG, L.; FINDEISEN, M.; GIESA, S.; MÜLLER, D.; WELZEL, P. *Tetrahedron* **2001**, 57, 9737.
- 106 OGURI, H.; SASAKI, S.; OISHI, T.; HIRAMA, M. *Tetrahedron Lett.* **1999**, 40, 5405.
- 107 McDONALD, F. E.; WEI, X. *Org. Lett.* **2002**, 4, 593.
- 108 TROST, B. M.; GUNZNER, J. L.; DIRAT, O.; RHEE, Y. H. *J. Am. Chem. Soc.* **2002**, 124, 10396.
- 109 BOUZBOUZ, S.; COSSY, J. *Org. Lett.* **2001**, 3, 1451.
- 110 FORGET-CHAMPAGNE, D.; MONDON, M.; FONTENEAU, N.; GESSON, J.-P. *Tetrahedron Lett.* **2001**, 42, 7229.
- 111 WANG, Y.; ROMO, D. *Org. Lett.* **2002**, 4, 3231.
- 112 CHATTERJEE, A. K.; CHOI, T.-L.; SANDERS, D. P.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2003**, 125, in press.
- 113 (a) PIETRASZUK, C.; MARCINIEC, B.; FISCHER, H. *Organometallics* **2000**, 19, 913; (b) KUJAWA-WELTEN, M.; PIETRASZUK, C.; MARCINIEC, B. *Organometallics* **2002**, 21, 840.

2.9

Olefin Metathesis Strategies in the Synthesis of Biologically Relevant Molecules

Jennifer A. Love

2.9.1

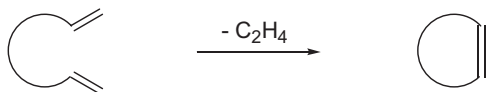
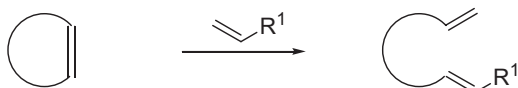
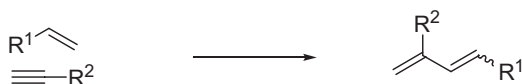
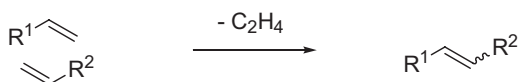
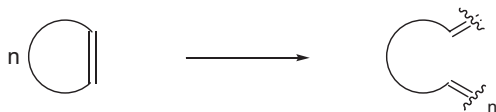
Introduction

Despite the remarkable success of current medicines for the treatment of human disease, new selective, therapeutic agents are still needed. Towards this goal, new medicinal leads are being generated to investigate the pharmacology of various bioactive molecules. These efforts require general accessibility of bioactive molecules and related structures, which depends upon the availability of suitable reaction methodology. As a result, many diverse strategies have been formulated for complex molecule synthesis. Among these, a few reactions have proven incredibly useful, including the Diels-Alder cycloaddition, the aldol reaction, and the Claisen rearrangement. Along these lines, olefin metathesis is emerging as one of the more powerful methods for carbon-carbon bond formation because of the exceptional versatility of this reaction and the availability of user-friendly catalysts. The utility of the metathesis reaction is increasingly apparent by its incorporation into many different complex molecule syntheses. This chapter will describe some recent uses of metathesis for the synthesis of biologically relevant molecules [1]. The elegant applications of metathesis demonstrated by the groups of Danishefsky, Nicolaou and Martin are highlighted in separate vignettes in this volume [2, 3].

2.9.1.1

Olefin Metathesis Strategies in Complex Molecule Synthesis

Several olefin metathesis processes have been used in the construction of complex molecules (Scheme 2.9-1). Of these, ring-closing metathesis (RCM), has been most extensively employed, based on the ability of metathesis to allow formation of many ring sizes, from 5-membered rings to macrocycles of greater than 20 atoms [4]. The formation of the ring is accompanied by the production of an equivalent of ethylene, which is readily removed from the desired products. In addition to RCM, ring cleavage through ring-opening metathesis (ROM), acyclic cross-coupling through olefin cross-metathesis (CM), and intra- and intermolecular ene-yne metathesis are receiving increasing attention as viable synthetic strategies. Ring-

Ring-Closing Metathesis (RCM)*Ring-Opening Metathesis (ROM)**Ene-Yne Metathesis**Cross Metathesis (CM)**Ring-Opening Metathesis Polymerization (ROMP)***Scheme 2.9-1.** Olefin metathesis processes.

opening metathesis polymerization (ROMP) has been used to construct polymeric materials with a range of properties, including those with biological activity.

2.9.1.2

Catalysts for Olefin Metathesis

A variety of olefin metathesis catalysts have been developed over the past 15 years. For example, the molybdenum-based catalyst **I** exhibits high olefin metathesis activity but lacks general functional group and environmental tolerance (Figure 2.9-1) [5]. In comparison, the “first-generation” ruthenium-based bis(phosphine) catalyst **II** is less active than **I** in metathesis reactions, but has significantly improved functional group compatibility [6]. More recently, strongly donating *N*-heterocyclic carbenes have been employed as ligands for ruthenium olefin metathesis catalysts. The resulting “second-generation” catalysts **III** [7] and **IV** [8] ex-

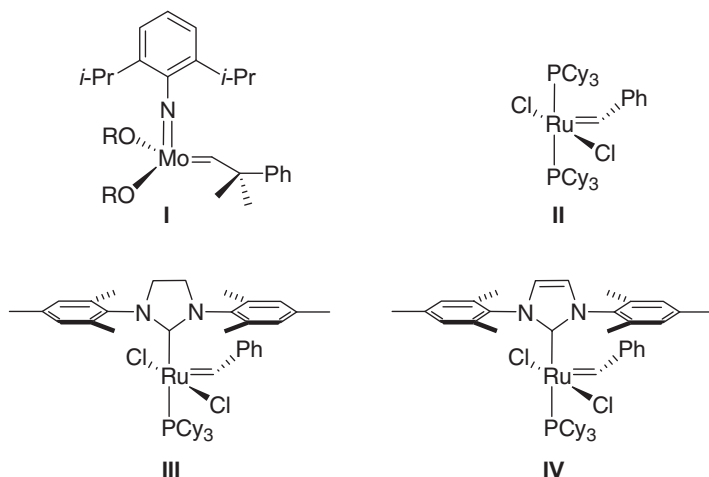


Fig. 2.9-1. Commonly encountered olefin metathesis catalysts.

hibit activity comparable to catalyst **I** and retain the functional group tolerance typical of late-metal systems. Such functional group compatibility is critical in complex molecule synthesis, and catalysts **II–IV** thus have been utilized in synthesis to a greater extent than **I**.

2.9.2

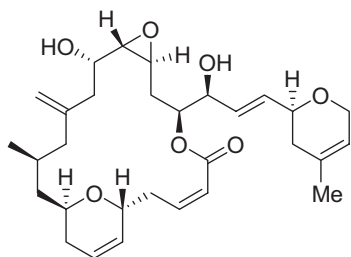
RCM and ROM in Complex Molecule Synthesis

Few general C–C bond-forming methods exist for the construction of macrocyclic rings. Notable examples include olefination reactions, such as Julia coupling and Wittig-type reactions, and metal-mediated methods, such as Heck, Stille, and Suzuki couplings and ene-yne cyclizations. A particularly remarkable feature of olefin metathesis relative to other C–C bond-forming processes is that metathesis allows straightforward construction of a wide range of ring sizes, including macrocycles. This section will detail the use of RCM to form 5- to 20-membered rings in the synthesis of biologically relevant target molecules. In certain cases, ROM will also be discussed as a relevant alternative to RCM.

2.9.2.1

Laulimalide

Laulimalide (**2.1**, Figure 2.9-2), a 20-membered macrolide isolated from marine sponges, shows potent cytotoxicity against several cancer cell lines, including the multi-drug-resistant cell line SKVLB-1. Recent studies have revealed that laulimalide effects microtubule stabilization, similar to the mechanism of action of taxol, epothilone, discodermolide, and eleutherobin, making this a promising therapeutic lead.



2.1

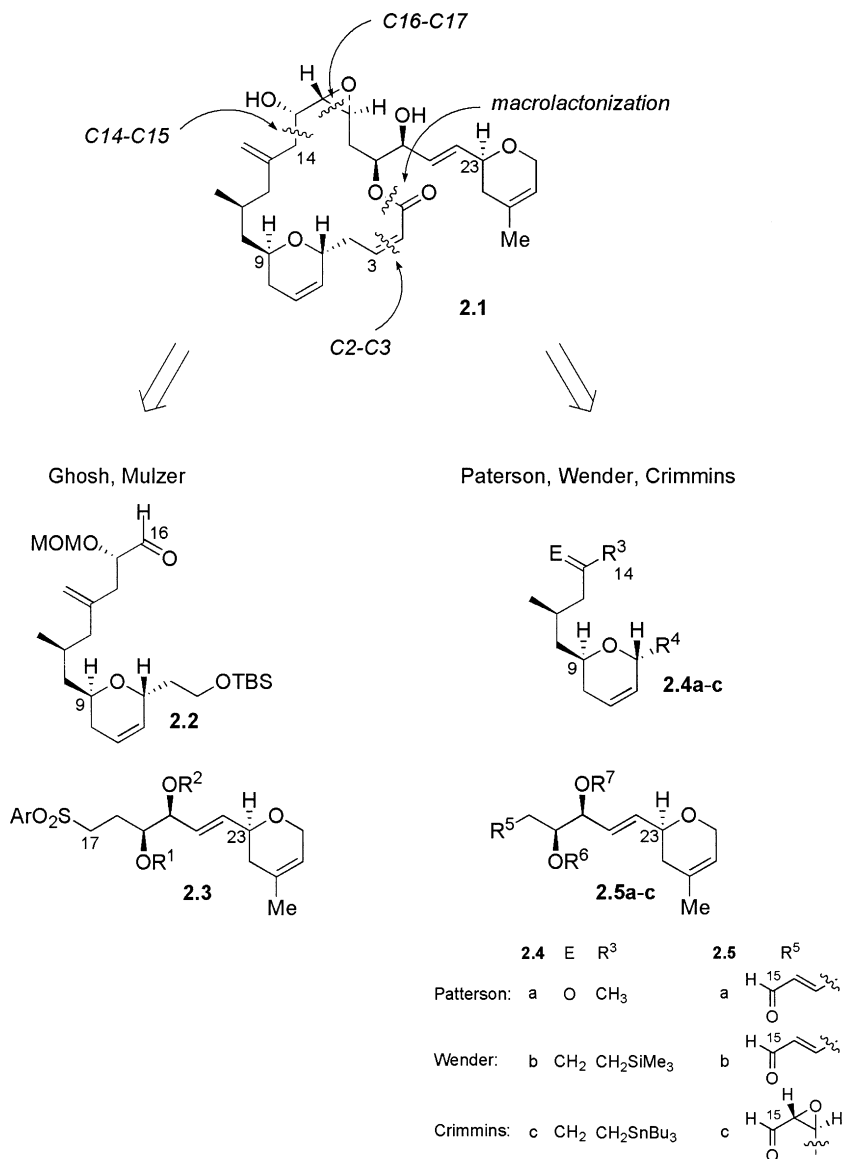
Fig. 2.9-2. Structure of laulimalide.

In light of this clinical potential, laulimalide has been the subject of intense synthetic effort over the past several years. The macrocyclic ring structure, two dihydropyran rings, and nine stereocenters render laulimalide a significant synthetic challenge. All five reported syntheses rely on the coupling of two fragments, each containing one of the dihydropyran rings, followed by macrocyclization. The syntheses by Ghosh [9] and Mulzer [10, 11] use Julia-Kocienski coupling of fragments **2.2** and **2.3** to form the C16–C17 bond and Horner-Emmons macrocyclic olefination to form the C2–C3 bond (Scheme 2.9-2). Paterson [12], Wender [13], and Crimmins [14] couple fragments **2.4** and **2.5** to form the C14–C15 bond and use macrolactonization to obtain the framework of laulimalide. Paterson employs a boron aldol reaction to couple the fragments, whereas Wender and Crimmins use allyl silane and allyl stannane additions, respectively. Attempts to use RCM to construct the macrocycle were unsuccessful with catalyst **II**, although this approach could be revisited using the more active catalysts **III** or **IV**.

Three of the syntheses employ metathesis to construct both dihydropyran rings. RCM is ideally suited to construct rings such as these that lack convenient functional group handles. In Ghosh's synthesis, RCM of diene **2.6** with bis(phosphine) catalyst **II** and $\text{Ti}(\text{O}-i\text{Pr})_4$ proceeds readily to provide lactone **2.7**, which is elaborated into fragment **2.2** (Scheme 2.9-3). In order for RCM of **2.6** to occur with the first-generation ruthenium catalyst **II**, a Lewis-acid co-catalyst ($\text{Ti}(\text{O}-i\text{Pr})_4$) is required to attenuate the electronics of the enone. Fragment **2.3** is assembled by elaboration of **2.9**, which is obtained in good yield by RCM of **2.8** to form the tri-substituted alkene product. The longest linear sequence is 25 steps (from a synthetic precursor).

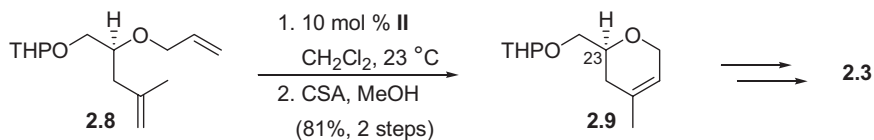
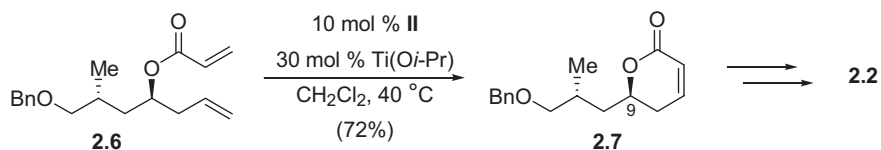
Mulzer assembles fragment **2.2** using RCM of acetal **2.10** to provide lactol derivative **2.11** in high yield (Scheme 2.9-4). By using an RCM precursor with a suitably protected carbonyl, the requirement for a Lewis-acid co-catalyst is avoided. RCM of **2.12** provides a high yield of **2.13**, which is subsequently converted to **2.3**. The longest linear sequence is 25 steps (from a synthetic precursor).

In Crimmins' synthesis, **2.14** undergoes efficient RCM to provide **2.15** in high yield (Scheme 2.9-5). The exclusive formation of **2.15** is consistent with an entropic preference for formation of the 6-membered ring relative to the other possible ring

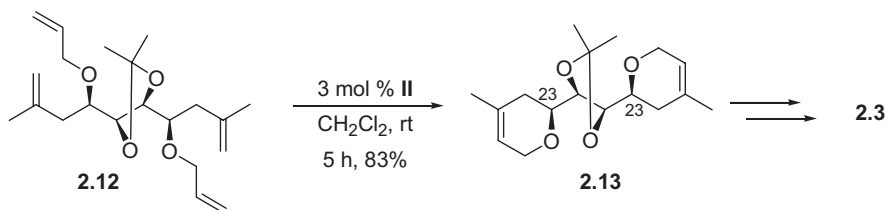
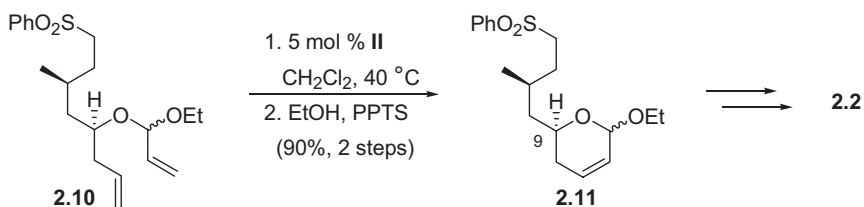


Scheme 2.9-2. Strategies for the synthesis of laulimalide.

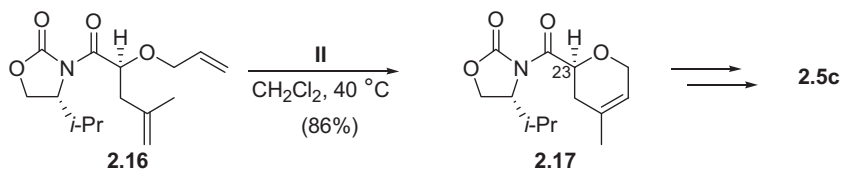
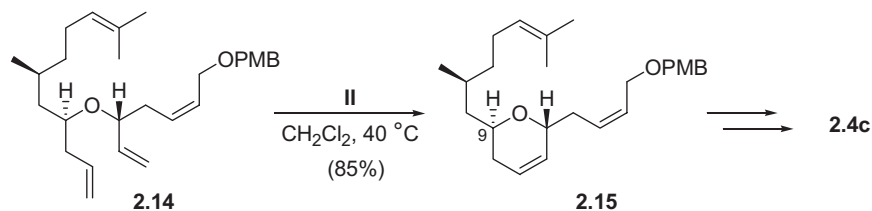
sizes. In addition, the lack of Z-olefin isomerization of the allylic ether of **2.14** indicates that the terminal olefins are more reactive than either the di- or trisubstituted olefins. Dihydropyran is subsequently transformed into fragment **2.4c**. The other fragment is generated by elaboration of **2.17**, obtained in high yield



Scheme 2.9-3. RCM in Ghosh's synthesis of laulimalide.



Scheme 2.9-4. RCM in Mulzer's synthesis of laulimalide.



Scheme 2.9-5. RCM in Crimmins' synthesis of laulimalide.

from RCM of **2.16**. The longest linear sequence is 20 steps (from a commercial precursor).

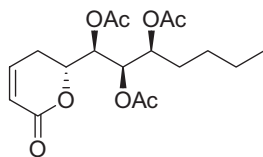
In comparison, two other groups use non-metathesis protocols to generate the 6-membered rings. Paterson uses boron aldol methodology to install the dihydropyran ring of fragment **2.4a** and a hetero-Diels-Alder reaction to generate the dihydropyran ring of **2.4b**; laulimalide is achieved in 27 steps (longest linear sequence from a synthetic precursor). Wender constructs both dihydropyran rings using hetero-Diels-Alder reactions; laulimalide is prepared in 25 steps (longest linear sequence from a commercial precursor). Overall, RCM compares favorably with these more established methods for construction of the dihydropyran rings.

2.9.2.2

Boronolide

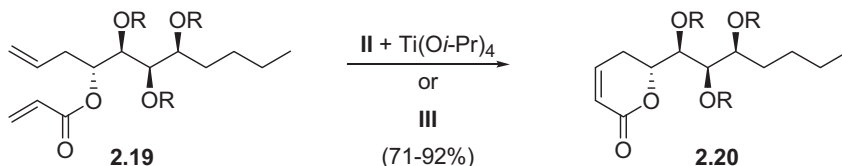
Polyhydroxylated natural products exhibit a wealth of both structural diversity and biological activity and have thus received considerable attention from synthetic chemists. For example, (+)-boronolide (**2.18**, Figure 2.9-3) is a polyacetoxylated δ -lactone isolated from the African shrubs *Tetradenai fruticoso* and *T. barberae* that has been used as an anti-malarial agent and has also been used in folk medicine [15]. Several asymmetric syntheses of boronolide have been reported [16], although most recently RCM has been recognized as a viable strategy for construction of the 6-membered lactone ring by three research groups [17–19].

All three of these syntheses utilize a similar ring-closing precursor with the general structure **2.19** (Scheme 2.9-6). Ghosh prepares **2.19** from tartrate, whereas Trost and Carda use direct aldol and boron aldol methodology, respectively. Ghosh and Carda use **II** to effect RCM, providing product in 84% and 71% yields, respectively. Catalytic $\text{Ti}(\text{O}-i\text{Pr})_4$ is necessary to promote metathesis of enone **2.19** in the presence of the first-generation catalyst **II**. In comparison, Trost recognized that **III** is considerably more active than **II** for metathesis of electron-deficient olefins.

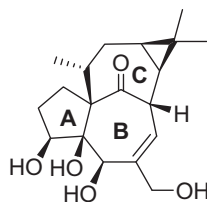


2.18

Fig. 2.9-3. Structure of (+)-boronolide.



Scheme 2.9-6. Metathesis approaches to the synthesis of (+)-boronolide.



2.21

Fig. 2.9-4. Structure of ingenol.

Accordingly, RCM of **2.19** in the presence of **III** provides **2.20** in 92% yield without the addition of a Lewis-acid co-catalyst.

2.9.2.3

Ingenol

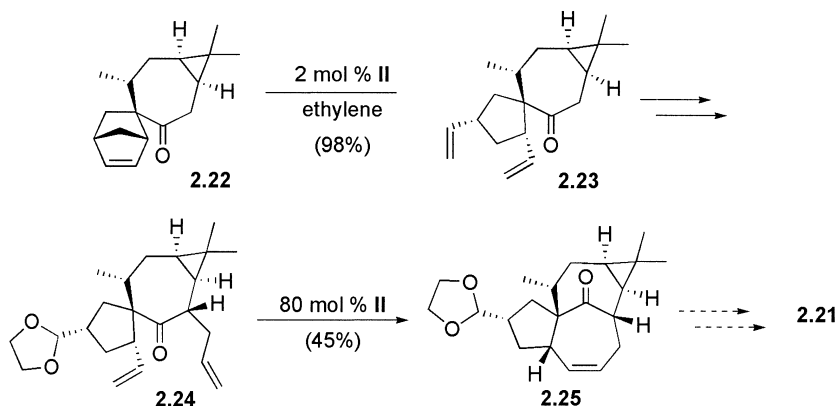
Ingenol (**2.21**, Figure 2.9-4) is a highly oxygenated diterpene that contains an unusual and tremendously strained inside-outside intrabridgehead stereochemistry of the BC ring. Certain ingenol esters are activators of protein kinase C (PKC) and many have anti-leukemia and anti-HIV activity [20]. The unique structural complexity of ingenol, coupled with its biological activity, makes this a desirable target for total synthesis.

In comparison to the myriad reactions available for synthesis of 6-membered rings, general methods for 7-membered ring construction are considerably less common [21]. The highly functionalized and strained structure of ingenol presents a particularly difficult synthetic challenge. Consequently, only the Winkler group has completed a total synthesis of ingenol despite the efforts of many other groups over nearly 20 years [22]. This approach relies on a photocycloaddition/fragmentation strategy to assemble the carbocyclic ingenol core. In comparison, Wood has recently reported the construction of the complete carbocyclic framework using two different metathesis processes [23, 24]. First, ROM of **2.22** in the presence of ethylene provides an excellent yield of **2.23** with a low catalyst loading. This is one of the few examples where ROM is used in complex molecule synthesis. Intermediate **2.23** is further elaborated to intermediate **2.24**, which then undergoes RCM to generate **2.25** (Scheme 2.9-7). The ability to use metathesis to construct the highly strained in/out ring system of ingenol compensates for the high catalyst loading and low yield of this reaction. Completion of the synthesis from advanced intermediate **2.25** is currently in progress.

2.9.2.4

Asteriscanolide

(+)-Asteriscanolide is a sesquiterpene lactone containing an unusual [6.3.0] ring skeleton (Figure 2.9-5). The challenges associated with the construction of 8-



Scheme 2.9-7. Wood's approach to the complete carbocyclic core of ingenol.

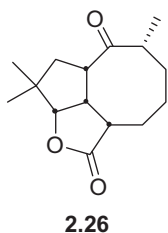
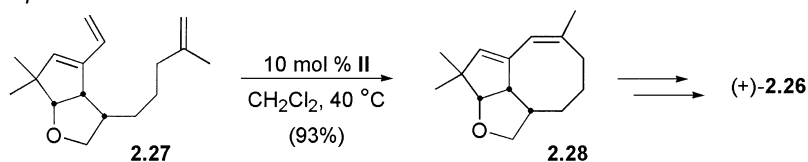
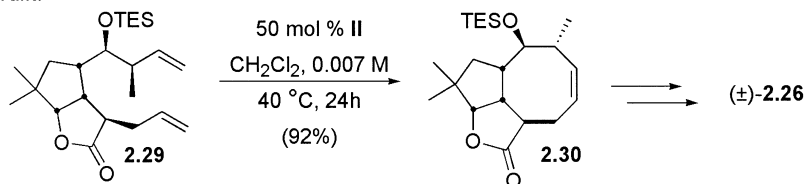
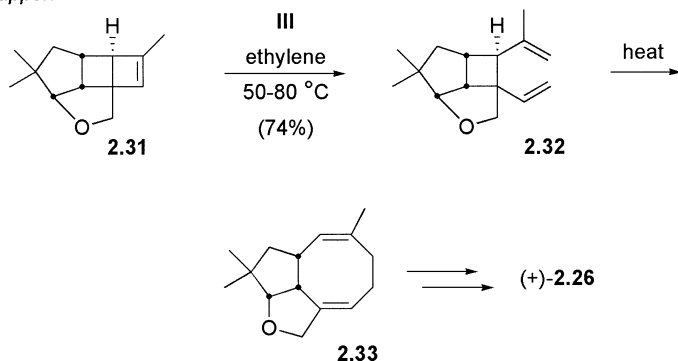


Fig. 2.9-5. Structure of (+)-asteriscanolide.

membered rings have contributed to the abundant interest in the synthesis of asteriscanolide. Although this molecule does not have significant biological activity, the lessons learned from its synthesis could be widely applicable to the construction of biologically important 8-membered ring natural products, such as taxol. Toward this goal, the Wender group reported the first and shortest route to (+)-asteriscanolide, employing a Ni-mediated [4+4] cycloaddition to construct the carbocyclic 5,8-ring system [25]. The second synthesis of asteriscanolide was not published until 12 years later [26], despite considerable research effort; since then, two additional syntheses have been reported [27, 28]. Most importantly, all three of these newer syntheses employ olefin metathesis (Scheme 2.9-8).

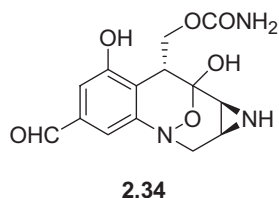
Two of the syntheses rely on RCM for construction of the 8-membered ring, providing a further proof of the power of metathesis in solving difficult synthetic problems. Paquette uses **II** to form the challenging trisubstituted olefin **2.28**, which is converted to (+)-**2.26** in four steps. Krafft was unable to obtain a similar trisubstituted olefin using either **I** or **II**. Instead, **2.29** was converted in high yield to **2.30**, which was transformed in three steps to (±)-**2.26**. Snapper uses a unique tandem strategy, coupling ROM with a Cope rearrangement. Intermediate **2.31** undergoes ROM in the presence of **III** and ethylene to generate **2.32**, which undergoes facile Cope rearrangement to provide **2.33**, that contains the 8-membered ring framework. (+)-**2.26** is obtained in three subsequent steps.

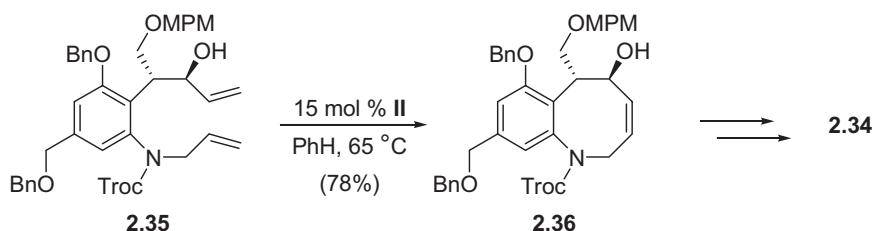
Paquette:*Krafft:**Snapper:***Scheme 2.9-8.** Syntheses of asteriscanolide via olefin metathesis.

2.9.2.5

(+)-FR900482

FR900482 (**2.34**) is a novel antitumor antibiotic that exhibits promising activity against several tumor cell lines [29, 30] (Figure 2.9-6). This molecule contains interesting structural features, including an aziridine, a carbamoyloxymethyl substituent, and a rare hydroxylamine hemiketal.

**Fig. 2.9-6.** Structure of (+)-FR900482.



Scheme 2.9-9. RCM in the formal synthesis of (+)-FR900482.

Despite the promising biological activity and unique structure of this molecule, only four syntheses have been reported [31–34]. Martin recently reported an enantioselective formal total synthesis of (+)-FR900482 using RCM of intermediate **2.35** to generate **2.36**, which is readily converted to an intermediate in Fukuyama's racemic synthesis (Scheme 2.9-9).

2.9.2.6

Salicylihalamide

Salicylihalamides A and B (**2.37**, Figure 2.9-7) were isolated from marine sponge sources and are thought to belong to a novel class of antitumor compounds, on the basis of pattern-recognition analyses performed at the NCI [35]. These molecules exhibit similar activity to the bafilomycins, which are mammalian vacuolar ATPase (V-ATPase) inhibitors. Irregular V-ATPase activity is thought to contribute to osteoporosis and various cancers. The mechanism of action of these compounds remains unknown and is being actively investigated. To facilitate these efforts, several research groups have initiated synthetic approaches to obtain adequate quantities of salicylihalamide and related analogues.

Five syntheses of salicylihalamide have been reported; all use macrocyclic RCM to form the 12-membered ring [36–40]. The first three syntheses, from De Brabander, Labreque, and Smith, established that the initial structural assignment was incorrect; these routes consequently produced *ent*-salicylihalamide. After structural revision, the De Brabander and Smith teams prepared natural salicylihalamide using strategies analogous to their initial approaches. The first four

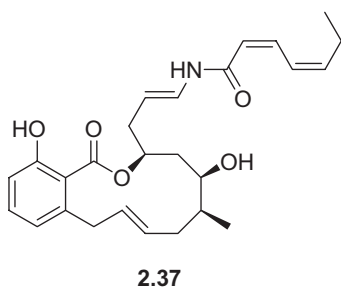
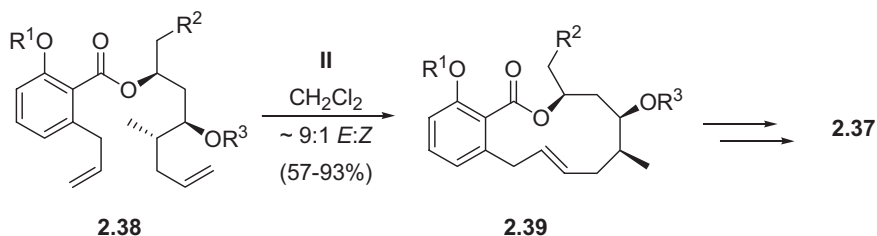
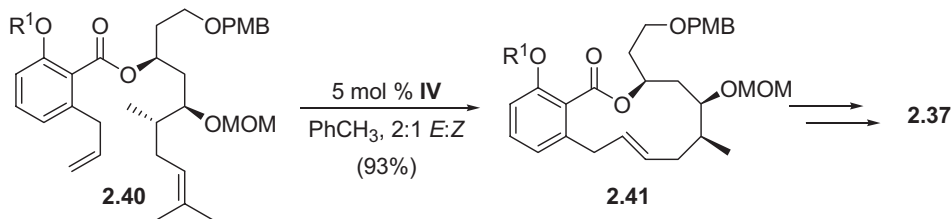


Fig. 2.9-7. Structure of salicylihalamide A.



Scheme 2.9-10. RCM approach to salicylilhalamide.



Scheme 2.9-11. Fürstner's approach to salicylilhalamide.

total syntheses all utilize intermediates that differ only in the extent of side chain incorporation and protecting group choice (Scheme 2.9-10). In each case, RCM of **2.38** in the presence of **II** provides **2.39** in high yield and with good *E:Z* selectivity. De Brabander and coworkers later used their metathesis route to develop a series of salicylilhalamide-like structures to probe structure-activity relationships. Their studies have revealed some highly potent analogues, which they are using to further probe the pharmacology of salicylilhalamide and related compounds.

Fürstner's synthesis uses an asymmetric reduction of a ketone to set absolute stereochemistry; the presence of a trisubstituted olefin was necessary to insure a high degree of chemoselectivity during this step. RCM of **2.40** required the more active second-generation catalyst **IV** because catalyst **II** was ineffective (Scheme 2.9-11). Interestingly, the use of a phenolic protecting group is critical to the stereochemical outcome of the metathesis reaction; an unprotected phenol ($R^1 = \text{H}$) gives exclusively the *Z*-isomer, whereas protection of the phenol ($R^1 = \text{TBS}$, MOM) allows access to the desired *E*-isomer. However, even in the best case, the *E:Z* control remains mediocre. Studies are in progress to elucidate the reasons for the pronounced dependence of olefin geometry on the choice of phenolic protecting group. However, this work nicely demonstrates the utility of the second-generation ruthenium-based catalysts for metathesis of sterically hindered olefins.

2.9.2.7

Roseophilin

Roseophilin (**2.42**, Figure 2.9-8) was isolated from the fermentation broth of *Streptomyces griseoviridis* and exhibits activity against leukemia and carcinoma cell lines [41]. Three syntheses of this molecule have been reported since its isolation in

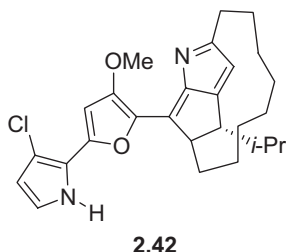
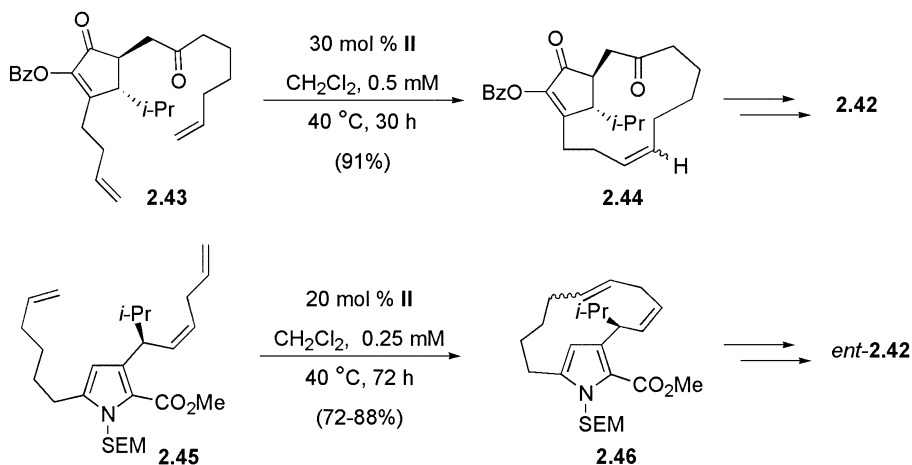


Fig. 2.9-8. Structure of (+)-roseophilin.



Scheme 2.9-12. RCM approaches to roseophilin.

1992 [42–45]. The first (racemic) synthesis from the Fürstner group uses a palladium-mediated allylic alkylation to form the 13-membered ring. Two subsequent asymmetric syntheses, from Tius and Boger, utilize macrocyclic RCM to produce natural (+)-roseophilin and unnatural *ent*-(–)-roseophilin, respectively. These syntheses served to unequivocally establish the absolute stereochemistry of the natural product.

In Tius's synthesis of roseophilin, RCM of **2.43** under highly dilute conditions provides **2.44** in high yield as a mixture of *E*- and *Z*-isomers (Scheme 2.9-12). Such dilute conditions are often required in macrocyclic RCM to prevent competing acyclic diene metathesis (ADMET) reactions. The pyrrole moiety of the natural product is installed at a later stage of the synthesis. In comparison, Boger installs the protected pyrrole moiety prior to RCM. In this case, diene **2.45** undergoes efficient RCM, also under highly dilute conditions, to provide **2.46** as an inconsequential 1:1 mixture of *E*- and *Z*-isomers. Only the 13-membered ring product is obtained during the reaction, presumably due to the sterically hindered environment around the internal olefin of **2.45**. The lack of isomerization of the *Z*-olefin of **2.45** supports this premise. Intermediate **2.46** is further elaborated to generate *ent*-

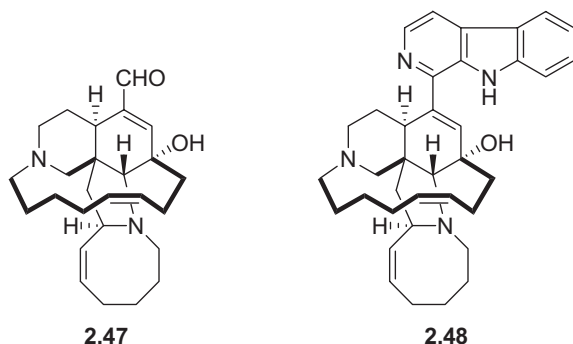


Fig. 2.9-9. Structures of ircinal A and manzamine A.

2.42. Both syntheses use low catalyst loadings, considering the entropic challenge of forming the 13-membered ring and that in each case there is little structural pre-organization for ring closing. It is noteworthy that Boger's biological studies indicate that *ent*-roseophilin is more potent than the natural isomer.

2.9.2.8

Ircinal A and Manzamine A

The manzamines are a family of indole alkaloids isolated from marine sponges. Manzamine A (2.48), the first member of this group to be isolated, exhibits potent antitumor, anti-malaria, and anti-tuberculosis activity [46]. A related alkaloid that shows similar activity, ircinal A (2.47), was isolated a short time later (Figure 2.9-9).

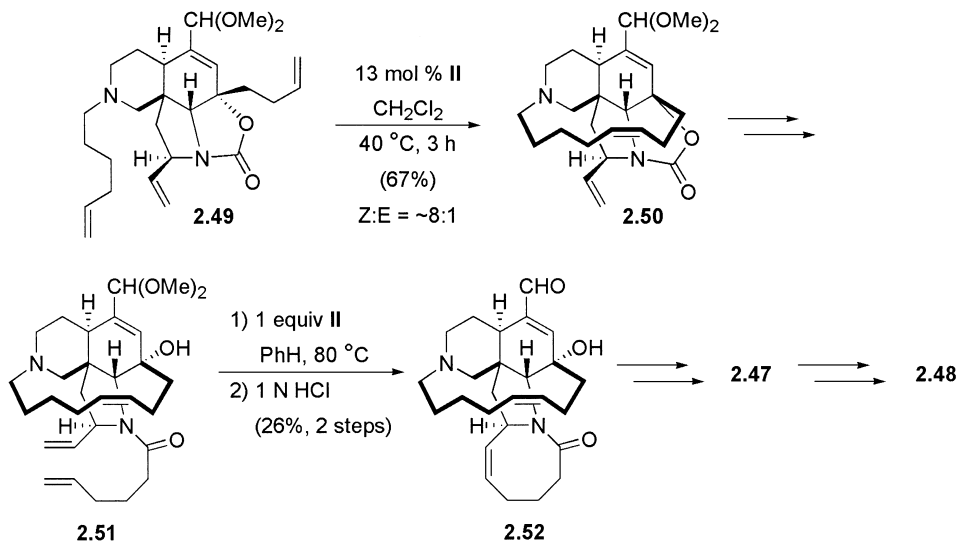
Martin and coworkers have developed a synthetic route to ircinal A using RCM to form both the 8- and 13-membered rings [47, 48]. RCM of late-stage intermediate 2.49 proceeds efficiently to provide a 67% yield of 2.50 (Scheme 2.9-13). Although 2.49 contains three olefins, only the desired reaction occurs, providing 2.50 with high (8:1) *Z:E* selectivity. The second metathesis step is performed on 2.51, which is obtained by hydrolysis of 2.50 and acylation of the resultant amine. Intermediate 2.51 undergoes RCM to provide 2.52, which is subsequently converted to ircinal A in two steps. Ircinal A is further converted to manzamine A in two additional steps [49].

Winkler has also reported the total synthesis of ircinal A, manzamine A, and related alkaloids by using vinylogous amide photocycloaddition/fragmentation/Mannich closure; [50] this work has been recently reviewed [51].

2.9.2.9

Amphidinolide A

The amphidinolides are a family of macrolides isolated from the marine dinoflagellate *Amphidinium* sp. that display a potent cytotoxicity against several cancer cell lines [52]. Amphidinolide A was the first of this family to be isolated and



Scheme 2.9-13. RCM reactions in the syntheses of ircinal A and manzamine A.

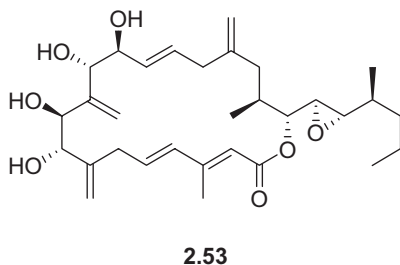


Fig. 2.9-10. Proposed structure of amphidinolide A.

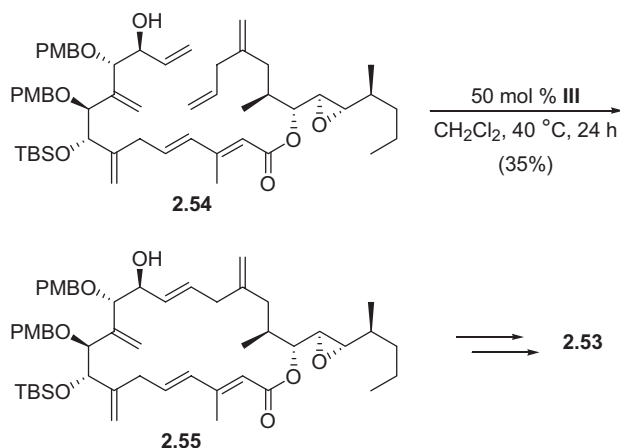
characterized; on the basis of NMR studies, amphidinolide A was assigned the structure shown in Figure 2.9-10 [53, 54].

Three recent total syntheses revealed that the proposed structure of amphidinolide A (2.53) is incorrect. Each of the syntheses uses a different organometallic macrocyclization strategy. Pattenden [55] employs a Pd-mediated sp^2 - sp^3 coupling reaction, and Trost [56] uses a Ru-mediated ene-yne cyclization. In Maleczka's approach, RCM forms the 20-membered ring (Scheme 2.9-14) [57]. Even though 2.54 contains multiple reactive double bonds, only *E*-2.55 was observed, albeit in modest yield.

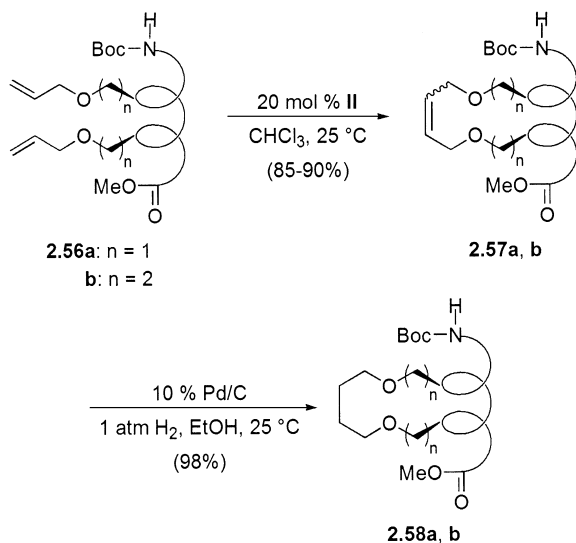
2.9.2.10

Peptidomimetics

Helices are common secondary structural motifs adopted by proteins. Efforts to decipher protein structure have sparked interest in generating helical peptidomi-



Scheme 2.9-14. Macrocyclic RCM in the synthesis of the proposed structure of amphidinolide A.



Scheme 2.9-15. RCM of helical peptides to form rigidified macrocyclic peptides with improved biostability.

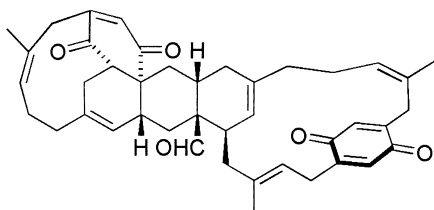
metics, often utilizing covalent or non-covalent linkages, such as salt bridges, disulfide bonds, and metal ligation, between amino acid residues. RCM has also been successfully used to generate macrocyclic peptide helices [58]. The peptide backbones of dienes **2.56a** and **2.56b** were shown to pre-organize in helical structures, facilitating RCM using catalyst **II** to provide **2.57a** and **2.57b**, respectively. Upon reduction, the resultant 21- and 23-membered macrocycles (**2.58a** and **b**) exhibit enhanced biostability [59].

2.9.3

Ring-Closing Ene-Yne Metathesis

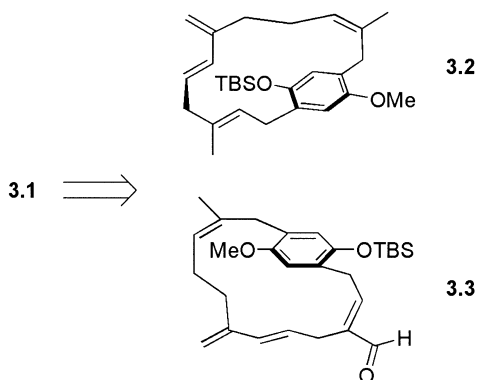
Ene-yne metathesis has been primarily used in the construction of small rings, but its use in macrocyclization has only recently been reported. Shair and coworkers recently reported the first synthesis of (–)-longithorone A (**3.1**, Figure 2.9-11) [60], a cytotoxic marine natural product with unusual structural features [61]. Longithorone A is assembled via a biomimetic Diels-Alder cycloaddition of fragments **3.2** and **3.3** (Scheme 2.9-16), which both are constructed by using ene-yne metathesis.

Reaction of **3.4** with **II** provides an inseparable 2.2:1 mixture of **3.5a** and **3.5b** (Scheme 2.9-17). The desired atropisomer is obtained with 20:1 selectivity, presumably due to its thermodynamic stability relative to the undesired isomer. Notably, product **3.5b** has lost an equivalent of propene, which has been previously observed in macrocyclic RCM [62]. Upon selective removal of the phenolic TBS protecting groups of the mixture of **3.5a** and **3.5b**, **3.6** is obtained as the exclusive product in 42% yield over two steps. Two additional steps are required for conversion of **3.6** into fragment **3.2**.

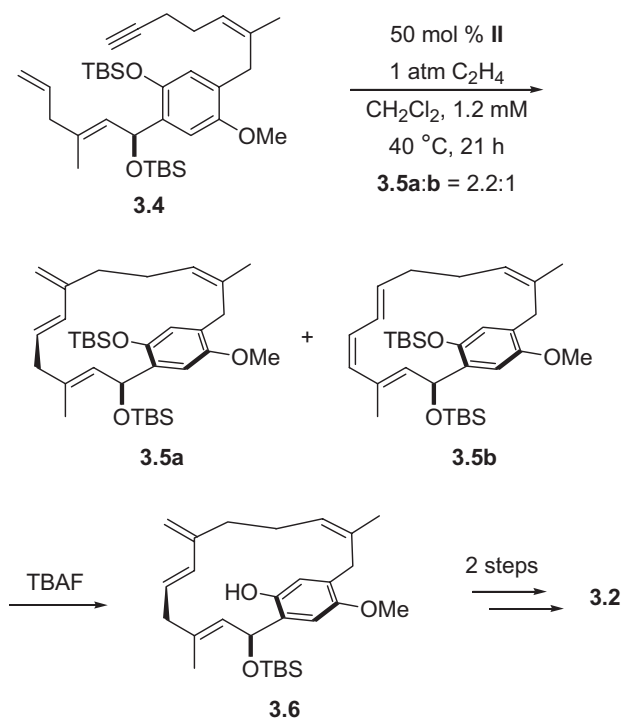


3.1

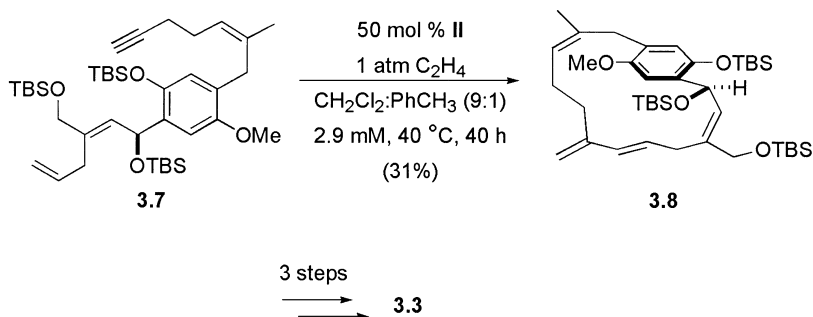
Fig. 2.9-11. Structure of (–)-longithorone A.



Scheme 2.9-16. Biomimetic cycloaddition strategy for the synthesis of (–)-longithorone A.



Scheme 2.9-17. Synthesis of fragment **3.2** via macrocyclic ene-yne metathesis.



Scheme 2.9-18. Synthesis of fragment **3.3** via macrocyclic ene-yne metathesis.

Fragment **3.3** is assembled as shown in Scheme 2.9-18. Metathesis of **3.7** provides a 31% yield of the desired atropisomer **3.8**, along with the corresponding *Z*-isomer as a minor byproduct. The atropdiastereoselectivity of this reaction is less than 3:1, which is substantially lower than that for the reaction of **3.4**. At this time, the reasons for this difference are unclear. Intermediate **3.8** is converted to **3.3** in three subsequent steps. Both ene-yne metathesis processes require the use of high loadings of **II**, which can be attributed to the entropic challenge of forming these rings.

2.9.4

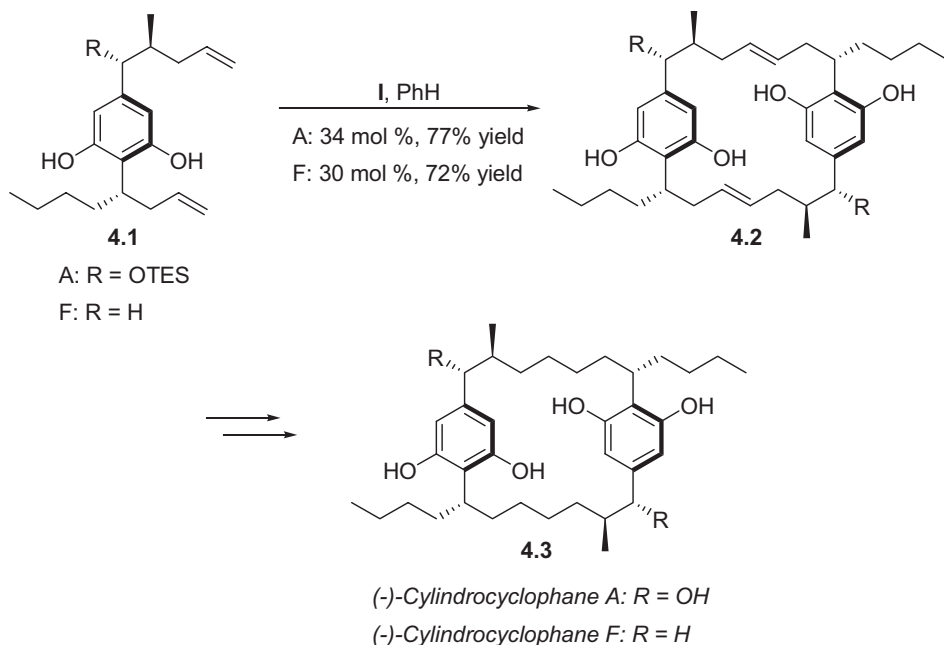
Cross-Metathesis in the Synthesis of Complex Molecules

Many natural products with biologically interesting properties contain highly functionalized alkyl chains, and an additional subset consists of entirely linear molecules. In these cases, RCM would obviously not be useful. Instead, ROM could be used to generate linear structures; however, this requires the synthesis of a functionalized cycloolefin that is subsequently obliterated. Another attractive possibility also exists: olefin cross-metathesis. CM has found increasing use in the construction of small molecules, although its use in complex molecule synthesis has begun only recently [63].

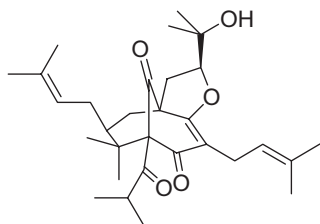
2.9.4.1

(–)-Cylindrocyclophanes A and F

Smith and coworkers recently demonstrated the use of a sequential CM/RCM strategy for the synthesis of cylindrocyclophanes A and F [64]. These molecules contain a 22-membered ring and display activity against several cancer cell lines. The [7,7]-paracyclophane structure of **4.2** is thermodynamically preferred over other possible isomers; because metathesis reactions are typically thermodynamically controlled processes, the desired structures are readily obtained in good yields under equilibrating conditions (Scheme 2.9-19).

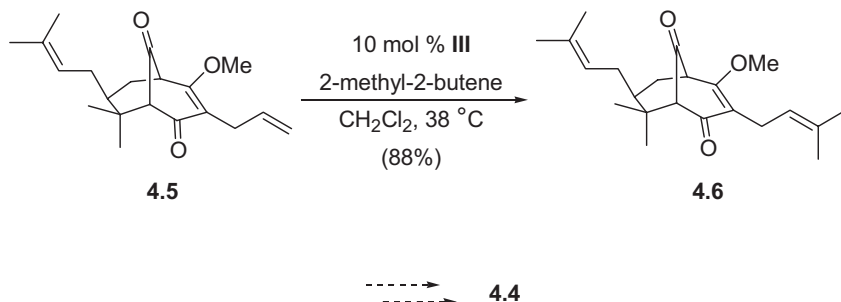


Scheme 2.9-19. CM/RCM strategy for the synthesis of cylindrocyclophanes A and F.



4.4

Fig. 2.9-12. Structure of garsubellin A.



Scheme 2.9-20. Use of CM for the synthesis of the carbocyclic core of garsubellin A.

2.9.4.2

Garsubellin A

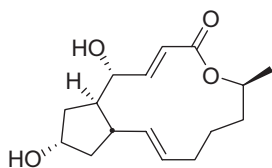
Recent studies have implicated reduced acetylcholine (ACh) levels in neurodegenerative diseases such as Alzheimer's [65]; consequently, a potential therapy for these diseases is to increase biosynthesis of ACh by stimulating choline acetyltransferase (ChAT) [66]. Garsubellin A (4.4, Figure 2.9-12), a polyprenylated phloroglucin isolated from *Garcinia subelliptica*, induces ChAT, thereby making this molecule an important synthetic target.

In studies directed toward the total synthesis of 4.4, Stoltz and Spessard have reported the use of a diastereoselective cyclization to generate the highly oxygenated [3.3.1] core in a single step [67]. After further elaboration, CM is used to install the second prenyl moiety [68]. In the presence of 2-methyl-2-butene, 4.5 is smoothly transformed to 4.6 (Scheme 2.9-20). Overall, this route provides the garsubellin A core in only 10 steps. Studies toward completion of the natural product are currently underway.

2.9.4.3

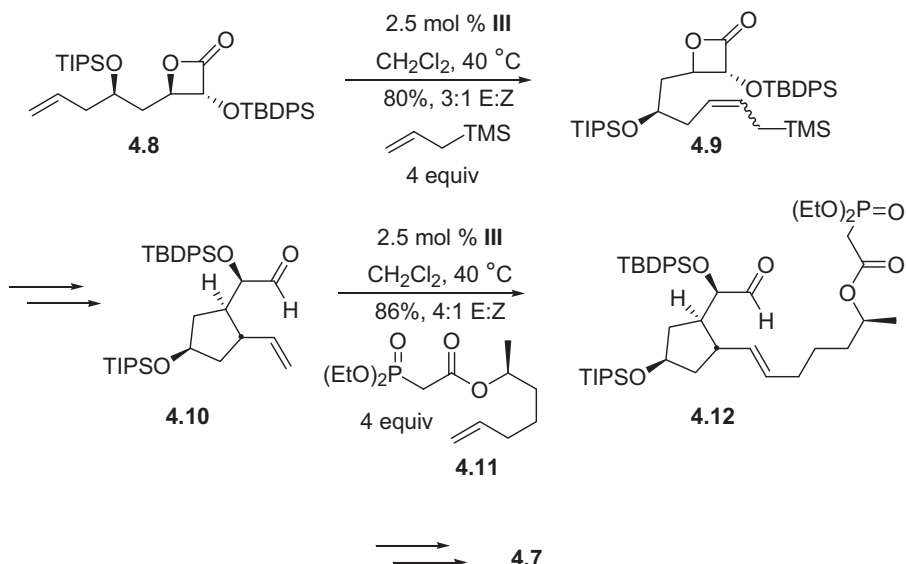
(+)-Brefeldin A

(+)-Brefeldin A (4.7, Figure 2.9-13) is a fungal metabolite with potent antitumor, antimitotic, antifungal, antiviral, and immunosuppressive activities [69]. As a



4.7

Fig. 2.9-13. Structure of (+)-brefeldin A.



Scheme 2.9-21. Synthesis of (+)-brefeldin A using CM.

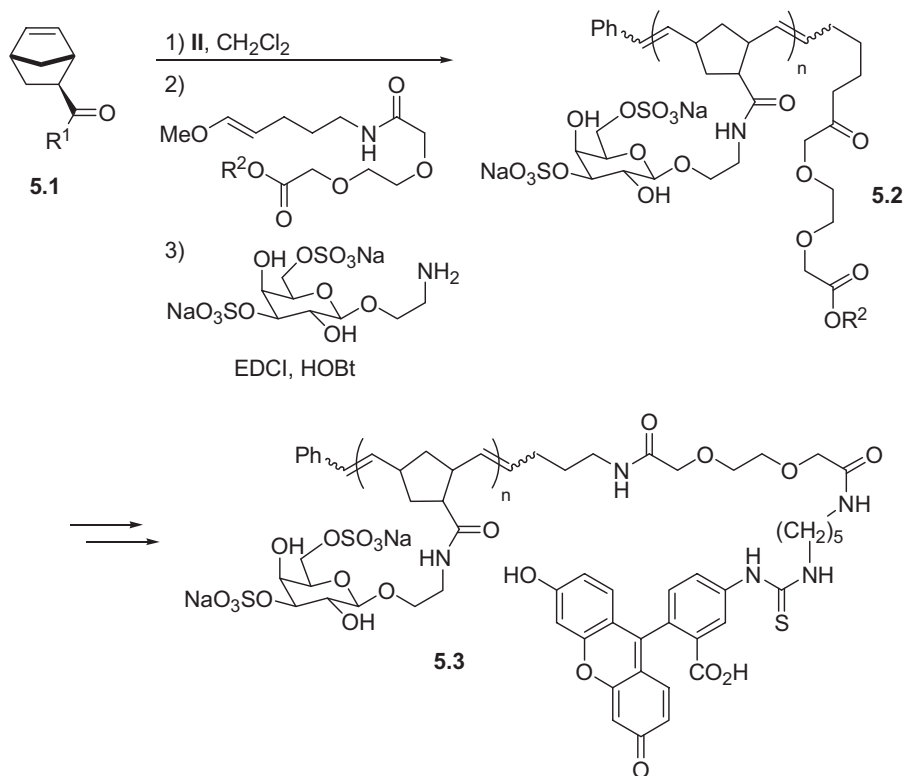
result, brefeldin A has been the subject of intense synthetic effort for the past two decades.

Romo recently reported the total synthesis of brefeldin A using two CM processes (Scheme 2.9-21) [70]. The first involves the reaction between **4.8** and allylsilane to give **4.9** in 80% yield as an inconsequential 3:1 mixture of *E*- and *Z*-isomers. Intermediate **4.9** is then converted to **4.10**, which undergoes efficient CM with alkenyl phosphonate **4.11** to provide **4.12** in 86% yield with 4:1 *E*:*Z* selectivity. Brefeldin A is completed by elaboration of **4.12**, including a Horner-Emmons macrocyclization to form the 13-membered ring.

2.9.5

ROMP in Complex Molecule Synthesis

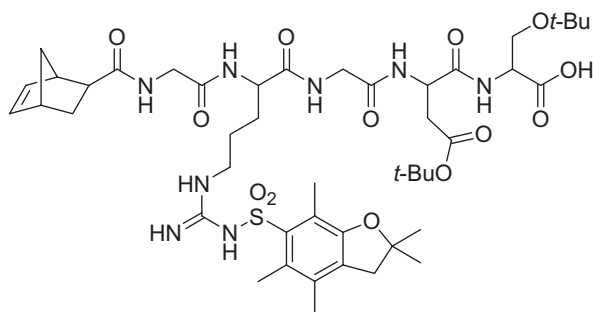
Multivalent binding occurs in several biologically important processes, including cell adhesion and immune response. Incorporating multiple ligands into a poly-



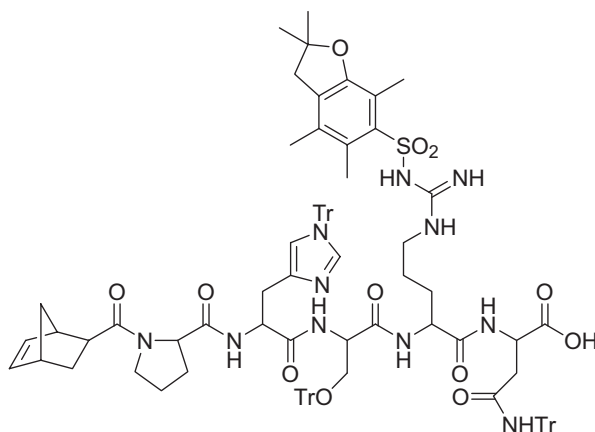
Scheme 2.9-22. Synthesis of biopolymer **5.3** based on a polynorbornene scaffold prepared using ROMP.

meric framework is an effective method for mimicking multivalent interactions [71]. Recognizing that ROMP is an effective method for construction of well-defined, highly functionalized polymers, Kiessling and coworkers have generated neoglycopolymers to probe multivalent binding events [72]. For example, biopolymers such as **5.3** that contain a fluorescent reporter group have been prepared by ROMP of norbornene derivatives (**5.1**, Scheme 2.9-22) [73]. These biopolymers have been used to study the stoichiometry of ligand-receptor binding events. These studies established that the multivalent ligands interact with multiple copies of L-selectin, which is a cell-surface protein involved in inflammation (see Chapter 3.6).

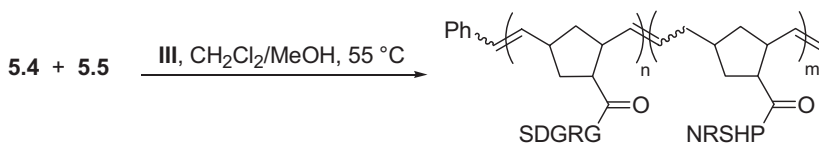
Norbornene-derived monomers can be substituted with other bioactive functionalities, including peptides. ROMP of two such monomers (**5.4** and **5.5**, Figure 2.9-14), substituted with the pentapeptide sequences GRGDS and PHSRN based on the integrin binding domain, provide polynorbornene copolymers (Scheme 2.9-23) that inhibit cell adhesion to the extracellular matrix protein fibronectin [74]. The presence of both peptide sequences was found to have a synergistic effect on the magnitude of inhibition.



5.4 (contains GRGDS sequence)



5.5 (contains PHSRN sequence)

Fig. 2.9-14. Norbornene monomers containing the pentapeptide sequences GRGDS and PHSRN.

5.6

Scheme 2.9-23. Polynorbornene copolymers containing the peptide sequences GRGDS and PHSRN.

2.9.6

Conclusions

Olefin metathesis has been successfully used to generate linear and cyclic structures, large and small rings, small molecules, and macromolecules. The incredible versatility, ease of execution, predictability, selectivity, and availability of stable

catalysts are the primary reasons that olefin metathesis has become one of the most widely used reactions in synthetic chemistry. The applications of metathesis will undoubtedly continue to grow as improved catalysts are developed and implemented. In particular, future advances in catalyst design are expected to improve catalyst loadings and yields in macrocyclization reactions. In addition, such advances are also expected to lead to control of olefin geometry and general methods for enantioselective metathesis processes.

References

- 1 The use of olefin metathesis in natural product synthesis has been previously reviewed: a) WRIGHT, D. L. *Curr. Org. Chem.* **1999**, 3, 211. b) CHANG, S.; GRUBBS, R. H. *Tetrahedron* **1998**, 54, 4413.
- 2 See vignette by J. T. NJARDARSON, R. M. GARBACCIO, AND S. J. DANISHEFSKY.
- 3 See vignette by K. C. NICOLAOU, AND S. A. SNYDER.
- 4 For early examples of the use of olefin metathesis in the construction of macrocycles, see: a) VILLEMIN, D. *Tetrahedron Lett.* **1980**, 21, 1715. (b) TSUJI, J.; HASHIGUCHI, S. *Tetrahedron Lett.* **1980**, 21, 2955.
- 5 a) SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DiMARE, M.; O'REGAN, M. J. *Am. Chem. Soc.* **1990**, 112, 3875. b) BAZAN, G. C.; KHOSRAVI, E.; SCHROCK, R. R.; FEAST, W. J.; GIBSON, V. C.; O'REGAN, M. B.; THOMAS, J. K.; DAVIS, W. M. J. *Am. Chem. Soc.* **1990**, 112, 8378. c) BAZAN, G. C.; OSKAM, J. H.; CHO, H.-N.; PARK, L. Y.; SCHROCK, R. R. J. *Am. Chem. Soc.* **1991**, 113, 6899.
- 6 a) SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2039. b) SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. J. *Am. Chem. Soc.* **1996**, 118, 100.
- 7 SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 953.
- 8 a) SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. *Tetrahedron Lett.* **1999**, 40, 2247. b) HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSEN, J. L. J. *Am. Chem. Soc.* **1999**, 121, 2674.
- 9 a) GHOSH, A. K.; WANG, Y. J. *Am. Chem. Soc.* **2000**, 122, 11027. b) GHOSH, A. K.; WANG, Y.; KIM, J. T. *J. Org. Chem.* **2001**, 66, 8973.
- 10 MULZER, J.; OHLER, E. *Angew. Chem. Int. Ed.* **2001**, 40, 3842.
- 11 In a subsequent approach, Enev and Mulzer report the formation of the C14–C15 bond using an allyl silane addition reaction. See: a) ENEV, V. S.; KAEHLIG, H.; MULZER, J. J. *Am. Chem. Soc.* **2001**, 123, 10764. b) MULZER, J.; OHLER, E.; ENEV, V. S.; HANBAUER, M. *Adv. Synth. Catal.* **2002**, 344, 573.
- 12 PATERSON, I.; DE SAVI, C.; TUDGE, M. *Org. Lett.* **2001**, 3, 3149.
- 13 WENDER, P. A.; HEGDE, S. G.; HUBBARD, R. D.; ZHANG, L. J. *Am. Chem. Soc.* **2002**, 124, 4956.
- 14 CRIMMINS, M. T.; STANTON, M. G.; ALLWEIN, S. P. J. *Am. Chem. Soc.* **2002**, 124, 5958.
- 15 a) FRANCA, N. C.; POLONSKY, J. C. *R. Acad. Sci. Paris* **1971**, 273, 439. b) DAVIS-COLEMAN, M. T.; RIVETT, D. E. *Phytochemistry* **1987**, 26, 3047. c) WATT, J. M.; BRANDWIJK, M. G. B. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*; Livingston: Edinburgh, 1962; p 516.
- 16 For total syntheses that do not use metathesis, see: a) NAGANO, H.; YASUI, H. *Chem. Lett.* **1992**, 1045. b) HONDA, T.; HORIUCHI, S.; MISUTANI, H.; KANAI, K. J. *Org. Chem.* **1996**, 61, 4944.
- 17 GHOSH, A. K.; BILCER, G. *Tetrahedron Lett.* **2000**, 41, 1003.
- 18 CARDIA, M.; RODRIGUEZ, S.; SEGOVIA, B.; MARCO, J. A. J. *Org. Chem.* **2002**, 67, 6560.
- 19 TROST, B. M.; YEH, V. S. C. *Org. Lett.* **2002**, 4, 3513.
- 20 a) HECKER, E. *Cancer Res.* **1968**, 28, 2338. b) HASLER, C. M.; ACS, G.;

- BLUMBERG, P. *Cancer Res.* **1992**, *52*, 202. c) HECKER, E. *Pure Appl. Chem.* **1977**, *49*, 1423–1431. d) KUPCHAN, S. M.; UCHIDA, I.; BRANFMAN, A. R.; DAILEY, R. G.; FEI, B. Y. *Science* **1976**, *191*, 571. e) FUJIWARA, M.; IJICHI, K.; TOKUHISA, K.; KATSUURA, K.; SHIGETA, S.; KONNO, K. *Antimicrob. Agents Chemother.* **1996**, *40*, 271–273.
- 21 WENDER, P. A.; LOVE, J. A. *Advances in Cycloaddition* **1999**, *5*, 1–45.
- 22 WINKLER, J. D.; ROUSE, M. B.; GREANEY, M. F.; HARRISON, S. J.; JEON, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726.
- 23 TANG, H.; YUSUFF, N.; WOOD, J. L. *Org. Lett.* **2001**, *3*, 1563.
- 24 For a different approach to the complete carbocyclic framework, see: a) FUNK, R. L.; OLMSTEAD, T. A.; PARVEZ, M. J. *Am. Chem. Soc.* **1988**, *110*, 3298. (b) FUNK, R.; OLMSTEAD, T. A.; PARVEZ, M.; STALLMAN, J. B. *J. Org. Chem.* **1993**, *58*, 5873.
- 25 WENDER, P. A.; IHLE, N. C.; CORREIA, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.
- 26 PAQUETTE, L. A.; TAE, J.; ARRINGTON, M. P.; SADOON, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742.
- 27 LIMANTO, J.; SNAPPER, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071.
- 28 KRAFFT, M. E.; CHANG, Y. Y.; ABOUD, K. A. *J. Org. Chem.* **2001**, *66*, 7443.
- 29 Isolation: IMANAKA, H.; AOKI, H.; KOHSAKA, M.; TERANO, H.; KIYOTO, S.; IWAMI, M. *J. Antibiot.* **1987**, *40*, 589.
- 30 Biological activity: a) KIKUCHI, H.; SHIMOMURA, K.; HIRAI, O.; MIZOTA, T.; MATSUMOTO, S.; MORI, J.; SHIBAYAMA, F. *J. Antibiot.* **1987**, *40*, 600. b) NAOE, Y.; INAMI, M.; MATSUMOTO, S.; TAKAGAKI, S.; FUJIWARA, T.; YAMAZAKI, S.; KAWAMURA, I.; NISHIGAKI, F.; TSUJIMOTO, S.; MANDA, T.; SHIMOMURA, K. *Jpn. J. Cancer Res.* **1998**, *89*, 1306.
- 31 FUKUYAMA, T.; XU, L.; GOTO, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.
- 32 DANISHEFSKY, S. J.; SCHKREYANTZ, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 4722.
- 33 a) TERASHIMA, S.; KATO, T.; ITOH, E.; YOSHINO, T.; HASHIMOTO, M.; NAGATA, Y. *Tetrahedron* **1997**, *53*, 10229–10238. b) TERASHIMA, S.; KATO, T.; ITOH, E.; YOSHINO, T.; HASHIMOTO, M.; NAGATA, Y. *Tetrahedron* **1997**, *53*, 10239–10252. c) TERASHIMA, S.; KATO, T.; ITOH, E.; YOSHINO, T.; NAGATA, Y.; NAKATANI, S. *Tetrahedron* **1997**, *53*, 10253–10270. d) KATO, T.; TERASHIMA, S. *J. Synth. Org. Chem., Jpn.* **1997**, *55*, 946–957.
- 34 FELLOWS, I.; KAEHLIN, D. E.; MARTIN, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781.
- 35 a) ERICKSON, K. L.; BEUTLER, J. A.; CARDELLINA, J. H., II; BOYD, M. R. *J. Org. Chem.* **1997**, *62*, 8188; correction: *J. Org. Chem.* **2001**, *66*, 1532. b) KUNZE, B.; JANSEN, R.; SASSE, F.; HOFLE, G.; REICHENBACH, H. J. *Antibiot.* **1998**, *51*, 1075. c) JANSEN, R.; KUNZE, B.; REICHENBACH, H.; HOFLE, G. *Eur. J. Org. Chem.* **2000**, 913–919.
- 36 a) WU, Y.; ESSER, L.; DE BRABANDER, J. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 4308. b) WU, Y.; LIAO, X.; WANG, R.; XIE, X.-S.; DE BRABANDER, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245.
- 37 LABRECQUE, D.; CHARRON, S.; REJ, R.; BLAIS, C.; LAMOTHE, S. *Tetrahedron Lett.* **2001**, *42*, 2645.
- 38 a) SMITH, A. B.; ZHENG, J. *Synlett* **2001**, 1019. b) SMITH, A. B.; ZHENG, J. *Tetrahedron* **2002**, *58*, 6455.
- 39 SNIDER, B. B.; SONG, F. *Org. Lett.* **2001**, *3*, 1817.
- 40 FÜRSTNER, A.; DIERKES, T.; THIEL, O. R.; BLANDA, G. *Chem. Eur. J.* **2001**, *7*, 5286.
- 41 HAYAKAWA, Y.; KAWAKAMI, K.; SETO, H.; FURIHATA, K. *Tetrahedron Lett.* **1992**, *33*, 2701.
- 42 FÜRSTNER, A.; WEINTRITT, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.
- 43 HARRINGTON, P. E.; TIUS, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509.
- 44 BOGER, D. L.; HONG, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.
- 45 For formal syntheses, see: a) HARRINGTON, P. E.; TIUS, M. A. *Org. Lett.* **1999**, *1*, 649. b) KIM, S. H.; FUCHS, P. L. *Tetrahedron Lett.* **1996**, *37*, 2545–2548. c) KIM, S. H.; FIGUEROA, I.; FUCHS, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601–2604. d) MOCHIZUKI, T.; ITOH, E.; SHIBATA, N.; NAKATANI, S.; KATO, T.; TERASHIMA, S. *Tetrahedron Lett.* **1998**, *39*, 6911. e) ROBERTSON, J.;

- HATLEY, R. J. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1455. f) BAMFORD, S. J.; LUKER, T.; SPECKAMP, W. N.; HIEMSTRA, H. *Org. Lett.* **2000**, 2, 1157. g) TROST, B. M.; DOHERTY, G. A. *J. Am. Chem. Soc.* **2000**, 122, 3801. h) ROBERTSON, J.; HATLEY, R. J. D.; WATKIN, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389.
- 46 For reviews, see: a) TSUDA, M.; KOBAYASHI, J. *Heterocycles* **1997**, 46, 765. b) MATZANKE, N.; GREGG, R.; WEINREB, S. *Org. Prep. Proc. Intl.* **1998**, 30, 1. c) MAGNIER, E.; LANGLOIS, Y. *Tetrahedron* **1998**, 54, 6201. d) ANG, K. K. H.; HOLMES, M. J.; HIGA, T.; HAMANN, M. T.; KARA, U. A. K. *Antimicrob. Agents Chemother.* **2000**, 44, 1645. e) EL SAYED, K. A.; KELLY, M.; KARA, U. A. K.; ANG, K. K. H.; KATSUYAMA, I.; DUNBAR, D. C.; KHAN, A. A.; HAMANN, M. T. *J. Am. Chem. Soc.* **2001**, 123, 1804.
- 47 a) MARTIN, S. F.; HUMPHREY, J. M.; ALI, A.; HILLIER, M. C. *J. Am. Chem. Soc.* **1999**, 121, 866. b) HUMPHREY, J. M.; LIAO, Y.; ALI, A.; REIN, T.; WONG, Y.-L.; CHEN, H.-J.; COURTNEY, A. K.; MARTIN, S. F. *J. Am. Chem. Soc.* **2002**, 124, 8584.
- 48 For a recent review of the use of RCM in alkaloid synthesis, see: PANDIT, U. K.; OVERKLEEF, H. S.; BORER, B. C.; BIERAUGEL, H. *Eur. J. Org. Chem.* **1999**, 959.
- 49 KONDO, K.; SHIGEMORI, H.; KIKUCHI, Y.; ISHIBASHI, M.; SASAKI, T.; KOBAYASHI, J. *J. Org. Chem.* **1992**, 57, 2480.
- 50 WINKLER, J. D.; AXTEN, J. M. *J. Am. Chem. Soc.* **1998**, 120, 6425.
- 51 BARRIAULT, L.; PAQUETTE, L. A. *Chemtracts* **1999**, 12, 276.
- 52 KOBAYASHI, J.; ISHIBASHI, M. *Chem. Rev.* **1993**, 93, 1753.
- 53 Isolation: KOBAYASHI, J.; ISHIBASHI, M.; NAKAMURA, H.; OHIZUMI, Y.; YAMASU, T.; SAKI, T.; HIRATA, Y. *Tetrahedron Lett.* **1986**, 27, 5755.
- 54 Structure: KOBAYASHI, J.; ISHIBASHI, M.; HIROTA, H. *J. Nat. Prod.* **1989**, 30, 4637.
- 55 LAM, H. W.; PATTENDEN, G. *Angew. Chem. Int. Ed.* **2002**, 41, 508.
- 56 TROST, B. M.; CHISHOLM, J. D.; WROBLESKI, S. J.; JUNG, M. *J. Am. Chem. Soc.* **2002**, 124, 12420.
- 57 MALECZKA, R. E.; TERRELL, L. R.; GENG, F.; WARD, J. S. *Org. Lett.* **2002**, 4, 2841.
- 58 a) BLACKWELL, H. E.; GRUBBS, R. H. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 3281. b) BLACKWELL, H. E.; SADOWSKY, J. D.; HOWARD, R. J.; SAMPSON, J. N.; CHAO, J. A.; STEINMETZ, W. E.; O'LEARY, D. J.; GRUBBS, R. H. *J. Org. Chem.* **2001**, 66, 5291.
- 59 For related studies, see: SCHAFMEISTER, C. E.; PO, J.; VERDINE, G. L. *J. Am. Chem. Soc.* **2000**, 122, 5891.
- 60 LAYTON, M. E.; MORALES, C. A.; SHAIR, M. D. *J. Am. Chem. Soc.* **2002**, 124, 773.
- 61 a) FU, X.; HOSSAIN, M. B.; SCHMITZ, F. J.; VAN DER HELM, D. *J. Org. Chem.* **1997**, 62, 3810. b) FU, X.; HOSSAIN, M. B.; VAN DER HELM, D.; SCHMITZ, F. J. *J. Am. Chem. Soc.* **2001**, 123, 8509.
- 62 JOE, D. AND OVERMAN, L. E. *Tetrahedron Lett.* **1997**, 38, 8635.
- 63 a) PEDERSON, R. L.; FELLOWS, I. M.; UNG, T. A.; ISHIHARA, H.; HAJELA, S. P. *Adv. Synth. Catal.* **2002**, 344, 728. b) PEDERSON, R. L. see chapter in this volume. c) CHATTERJEE, A. K.; see chapter in this volume.
- 64 SMITH, A. B.; ADAMS, C. M.; KOZMIN, S. A.; PAONE, D. V. *J. Am. Chem. Soc.* **2001**, 123, 5925.
- 65 *Fundamental Neuroscience*; ZIGMOND, M. J.; BLOOM, F. E.; LANDIS, S. C.; ROBERTS, J. L.; SQUIRE, L. R., Eds.; Academic Press: San Diego, 1999; pp 216–219.
- 66 AULD, D. S.; MENNICKEN, F.; DAY, J. C.; QUIRION, R. *J. Neurochemistry* **2001**, 77, 253.
- 67 SPESSARD, S. J.; STOLTZ, B. M. *Org. Lett.* **2002**, 4, 1943.
- 68 CHATTERJEE, A. K.; SANDERS, D. P.; GRUBBS, R. H. *Org. Lett.* **2002**, 4, 1939.
- 69 a) NUCHTERN, J. G.; BONIFACINO, J. S.; BIDDISON, W. E.; KLAUSNER, D. *Nature* **1989**, 339, 223. b) KLAUSNER, R. D.; DONALDSON, J. G.; LIPPINCOTT-SCHWARTZ, J. J. *Cell. Biol.* **1992**, 116, 1071.

- 70 WANG, Y.; ROMO, D. *Org. Lett.* **2002**, *4*, 3231.
- 71 For a review of polyvalent interactions, see: MAMMEN, M.; CHOI, S. K.; WHITESIDES, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754.
- 72 a) GORDON, E. J.; SANDERS, W. J.; KIESSLING, L. L. *Nature* **1998**, *392*, 30.
- b) MANNING, D. D.; STRONG, L. E.; HU, X.; BECK, P. J.; KIESSLING, L. L. *Tetrahedron* **1997**, *53*, 11937.
- 73 OWEN, R. M.; GESTWICKI, J. E.; YOUNG, T.; KIESSLING, L. L. *Org. Lett.* **2002**, *4*, 2293.
- 74 MAYNARD, H. D.; OKADA, S. Y.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 1275.

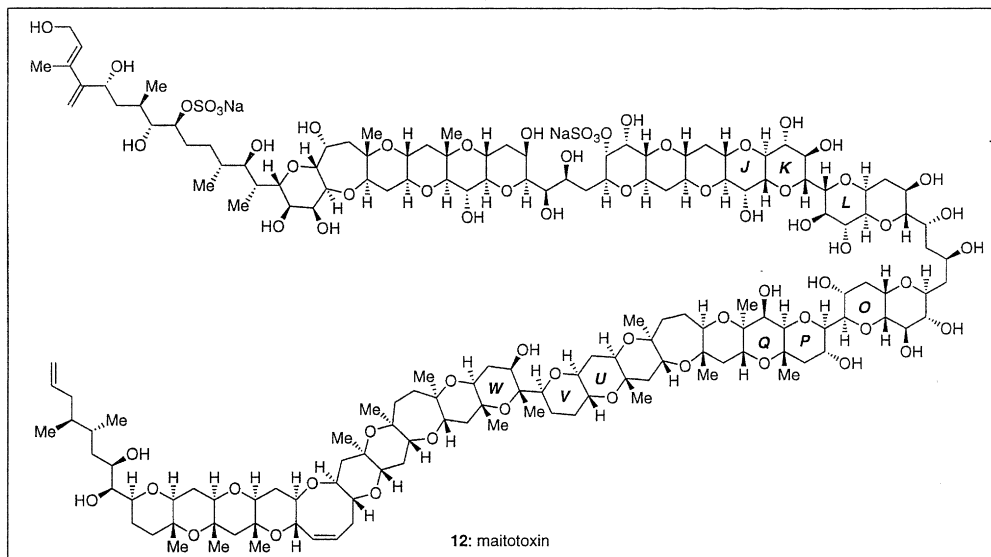
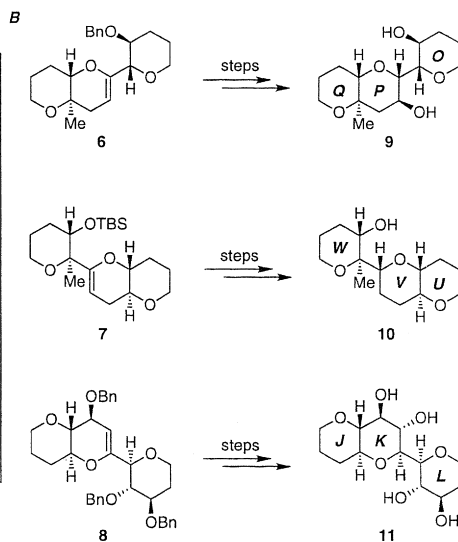
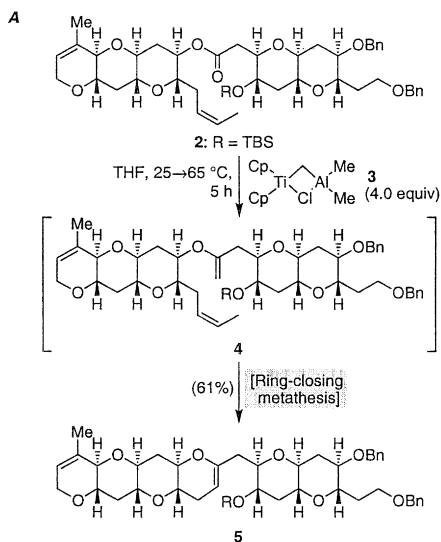
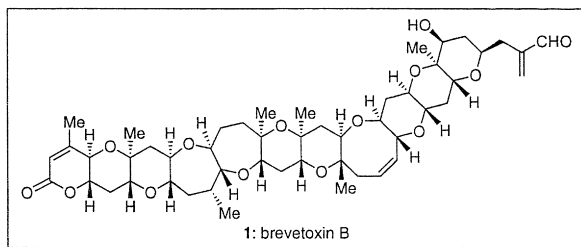
2.9 Vignette 1

The Olefin Metathesis Reaction in Complex Molecule Construction

K. C. Nicolaou and Scott A. Snyder

While our abilities as synthetic chemists have grown unabated since Wöhler's synthesis of urea in 1828, the history of that development is punctuated by a distinct set of seminal discoveries that have catalyzed significant shifts in how synthetic practitioners approach their science. Preeminent examples along these lines would certainly include the advent of the Diels–Alder cycloaddition in 1928 [1] and the Wittig reaction in 1953 [2]. Over the course of the past decade, we believe that a similar advance has occurred with the addition of olefin metathesis to the repertoire of synthetically useful transformations [3], as this process has significantly broadened and even altered the manner in which we currently approach synthetic strategy and design. Although several of the chapters in this text offer testimony that beautifully supports this statement, in this short vignette we hope to provide the final pieces of corroborative evidence by describing some of the dividends we have garnered upon application of the olefin metathesis reaction within our research programs directed towards the total synthesis of natural products. Our overall goal is not only to demonstrate the effectiveness of metathesis to fashion motifs that would otherwise be highly challenging to create, but also to illustrate the symbiotic relationship between catalyst development and subsequent applications in complex molecule construction.

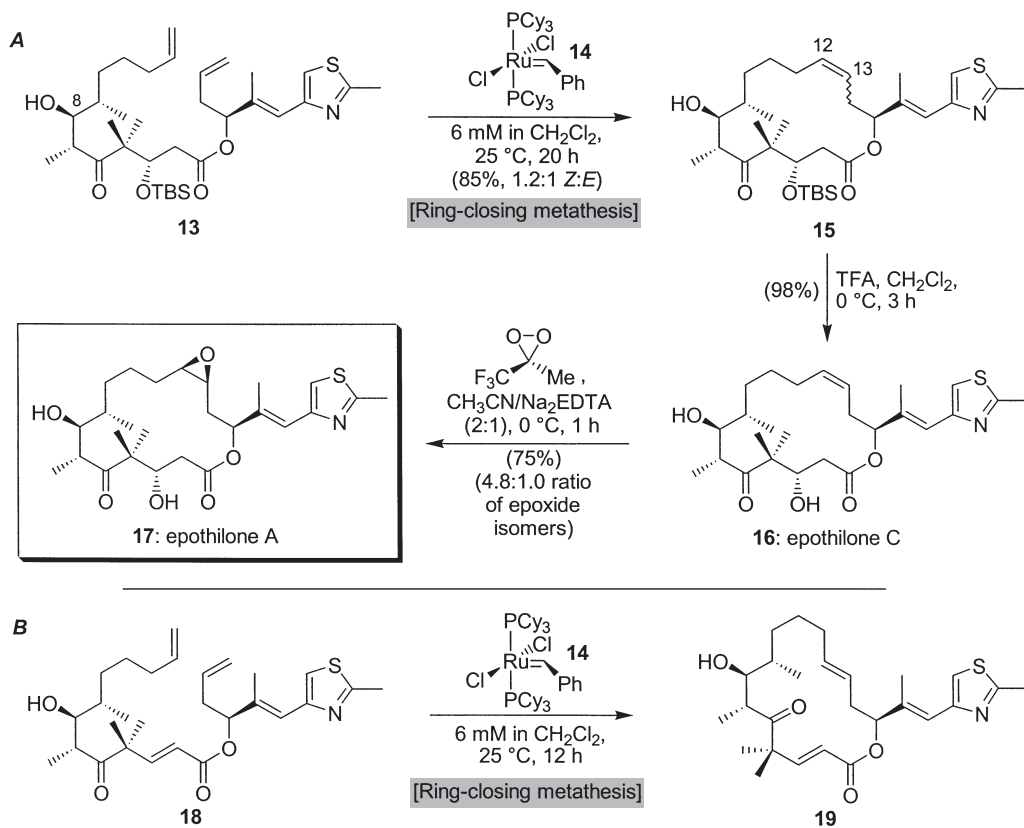
During early 1996, following the first string of reports in which olefin metathesis was used in contexts pertinent to the synthesis of highly functionalized molecules [4], we made known our opening contribution to the field through a disclosure in which metathesis was employed as a key step to fashion complex polyether frameworks representative of those possessed by numerous and diverse natural products, such as brevetoxin B (**1**, Scheme A.1-1) [5a]. In the designed strategy, upon reaction of **2** (Scheme A.1-1a) with stoichiometric amounts of the Tebbe reagent (**3**) [6], the methyldiene derived from this titanocene effected initial methylenation of the ester to generate an enol (**4**), as would be expected based on the established preference of this reagent to engage carbonyl functionality before attacking olefins. With excess Tebbe reagent in solution, however, subsequent ring-closing metathesis between the newly generated olefin and the neighboring alkene ensued, affording **5** in 61% yield. Having achieved success in this initial testing ground,



Scheme A.1-1. The synthesis of complex polyether frameworks via tandem methylenation/ring-closing metathesis: a) proof-of-principle; b) application to the OPQ, UVW, and JKL systems of maitotoxin.

the technology was subsequently applied to fashion **6**, **7**, and **8**, intermediates that ultimately were advanced to the QPO (**9**), WVU (**10**), and JKL (**11**) ring systems corresponding to frameworks within the structure of the complex marine natural product maitotoxin (**12**) [5b]. Overall, although this reaction process is not catalytic in metal, these examples constituted some of the earliest applications of metathesis to fashion polyethers, and, as a result, engendered confidence that the reaction could be applied productively in such contexts [7].

Inspired by this initial success, we were suitably encouraged a few months later to attempt a far more daring application of the olefin metathesis reaction as part of our research program directed toward the epothilones, potent antitumor agents isolated from the culture extract of the cellulose-degraded myxobacterium *Sorangium cellulosum* strain So ce90 [8]. Seeking to form the 16-membered macrocycle of epothilone A (**17**, Scheme A.1-2a) by a route other than macrolactonization, we anticipated that the power of ring-closing metathesis could potentially be employed to fashion the C12–C13 olefin in **15** from a precursor such as **13**. If successful, we

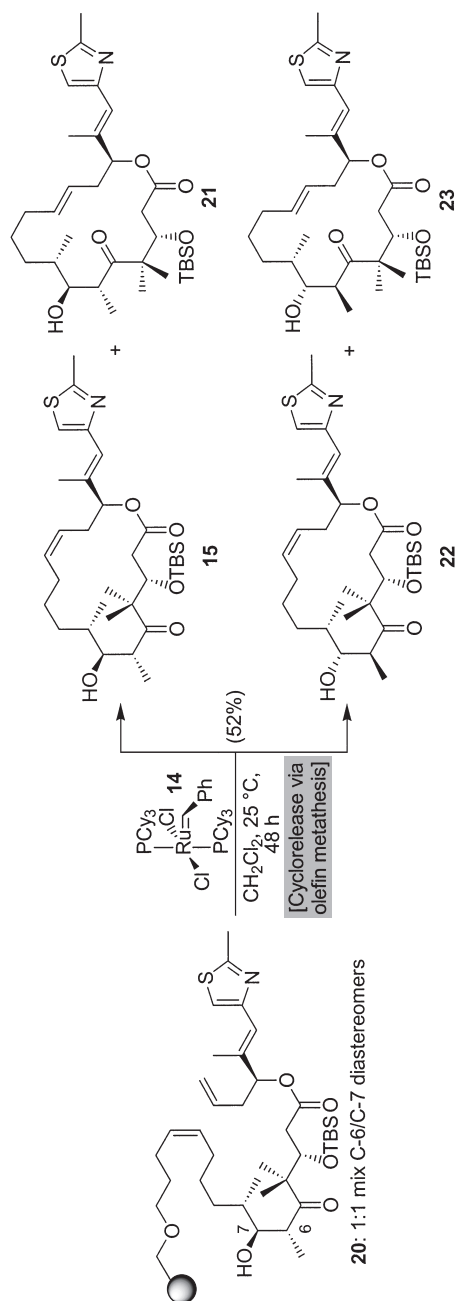


Scheme A.1-2. a) Ring-closing metathesis (RCM) to form the 16-membered macrocyclic system of epothilones A (**17**) and C (**16**); b) a model system showing the importance of the carbocyclic backbone composition in dictating the resultant stereoselectivity of RCM.

would have generated an intermediate that could be elaborated to **17** simply through a chemo- and stereoselective epoxidation reaction. Since these were the early days in the development of olefin metathesis in complex situations, however, at the outset of empirical studies several variables in the proposed transformation was unexplored territory in the metathesis landscape. First, it was uncertain whether or not the reaction could proceed with the thiazole side chain attached, since the Lewis basic nitrogen atom was positioned in proximity to one of the reacting olefins might coordinate with the catalyst itself or with an alkylidene intermediate and thereby shut down effective metathesis pathways. Additionally, the free C-8 hydroxyl group in **13**, which was left unprotected intentionally to minimize the number of protection/deprotection steps in the overall sequence, might also be a source of complications despite a precedent [9] suggesting that such functionality was tolerated by some of the newer (at that time) ruthenium-based catalyst systems such as **14** [10]. On top of these serious concerns, even if the reaction proved successful, it was uncertain whether the stereochemical outcome would favor the *Z*-olefin, as required for the epothilones, or the undesired *E*-isomer. Fortunately, these worries proved to be relatively unfounded, as exposure of **13** to a 10 mol % loading of Grubbs' ruthenium catalyst **14** in CH₂Cl₂ at ambient temperature for 20 hours effected macrocyclization to **15**, which was obtained as a 1.2:1 mixture of *Z:E* isomers in 85% yield [11].

Apart from eventually enabling the total synthesis of epothilones A and C, the more significant feature of this metathesis reaction was the overall *Z:E* selectivity of the conversion. While such product distributions are, of course, governed by thermodynamics, extensive studies based on the modification of reaction temperature or solvent afforded no useful levels of improvement in the ultimate geometrical mixture of **15** which was obtained. Unexpected was the degree to which modification of the array of functionality situated on the backbone of the eventual macrocyclic system dictated the *Z:E* ratio of the resultant olefinic products. For example, application of the same conditions as above to effect ring-closing metathesis of **18** (see Scheme A.1-2b), possessing $\Delta^{2,3}$ unsaturation in lieu of the C-3 stereocenter possessed by the natural product, led exclusively to the undesired *E*-isomer. Even though subsequent experimentation in numerous contexts has revealed that most metathesis-based macrocyclizations provide predominantly *E*-alkenes [12], the variability of these results for this family of natural products should serve as a reminder that we still lack the ability to reliably predict product geometry for certain ring-closing metathesis reactions in complex situations.

Despite the lack of control of the absolute stereocontrol in the formation of **15**, we viewed the creation of both *Z*- and *E*-olefins as a beneficial outcome, since it provided access to two distinct classes of macrocyclic epothilone analogues with which to probe the molecular basis for the potent biological activity inherent in this secondary metabolite. To facilitate such screening of diverse epothilone-like structural congeners, we next sought to extend our original metathesis approach to generate libraries of analogues by utilizing the power of split-and-pool combinatorial synthesis [13]. In this regard, we hoped to fashion an intermediate such as **20** (Scheme A.1-3), poised for a ring-closing metathesis reaction, in which the

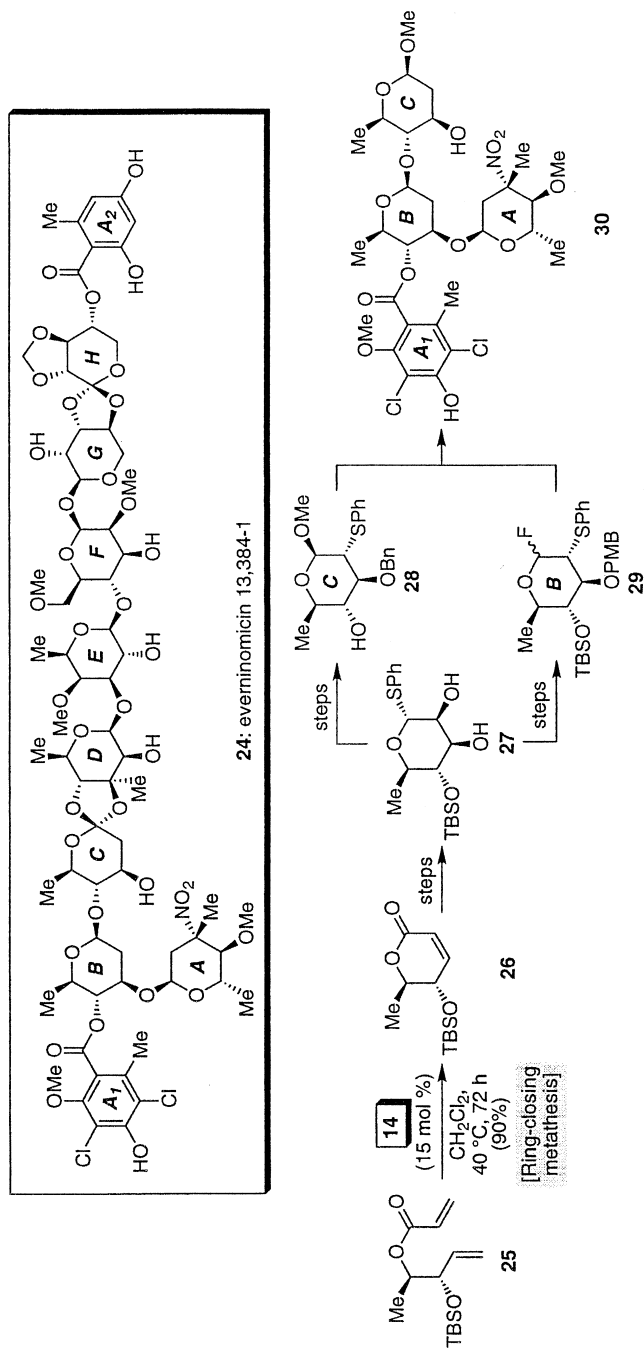


Scheme A.1-3. Solid-phase synthesis of epothilone A via a novel ring-closing metathesis cyclorelease strategy.

tether uniting the epothilone scaffold to the solid support was appended to the terminal position of one of the olefins that ultimately would participate in the key macrocycle-forming metathesis event. Although the increased steric hindrance imposed by incorporating the alkyl tether at this site might make metathesis more challenging to achieve, we felt that the benefits of linking in this manner would far outweigh any potential risk as ring closure would be attended by traceless release of the desired product from the resin, meaning no remnants of the original tether that joined the epothilone scaffold to the polystyrene support would remain. This result would be in contrast to most conventional solid-phase approaches, where some signature of the original tether (whether as a hydroxyl group or other functional handle) usually remains following cleavage. Perhaps more significant, appending the solid support in this mode would impart a safety feature to this cyclorelease strategy in that only material capable of undergoing metathesis would ultimately be freed from the resin. As such, any precursor that had not reacted properly during a step leading to **20** would remain attached, thereby ensuring that the products obtained from the metathesis reaction would not be contaminated with undesired byproducts.

This strategy proved relatively easy to explore because **20** was synthesized in short order; following exposure of this intermediate to alkylidene initiator **14** in CH₂Cl₂ at ambient temperature, the desired metathesis-based cyclorelease was indeed effected in 52% overall yield over the course of 2 days [14]. At the end of this event, a mixture of four products (**15**, **21**, **22**, and **23**) was isolated, whose formation resulted from the anticipated lack of *Z:E* selectivity in the metathesis step combined with a 1:1 mixture of C-6/C-7 diastereomers within the starting material (**20**) from an earlier aldol condensation. Fortunately, the polarity difference between these four compounds was sufficient to enable their separation by thin-layer chromatography (TLC) or high-pressure liquid chromatography (HPLC). Repetition of this sequence with novel building blocks then led to several hundred distinct analogues whose biological screening established a clear structure-activity profile for the epothilones, ultimately paving the way for the intelligent design of novel epothilone-like structures possessing comparable or even higher antitumor activities than the parent natural product [8].

Although the macrocyclic system of the epothilones clearly suggests ring-closing metathesis as a strategy to construct them, not all applications of this transformation in total synthesis are so obvious. In fact, many contexts in which metathesis could be utilized productively are obscured by the complexity of the target molecule. For example, during our early synthetic investigations targeting the highly intricate oligosaccharide antibiotic everninomicin 13,384-1 (**24**, Scheme A.1-4), we sought to develop a strategy that would enable the preparation of functionalized forms of both the B- and C-ring carbohydrate building blocks (for eventual glycosidations with other pieces) from a common intermediate [15]. While the array of functionalities present in these carbohydrates in their final format (**24**) does not reveal any obvious connection to a metathesis event, our retrosynthetic analysis suggested that both **28** and **29** could likely be constructed from **27**, a compound that in turn could be derived from α,β -unsaturated intermediate **26**. With sim-

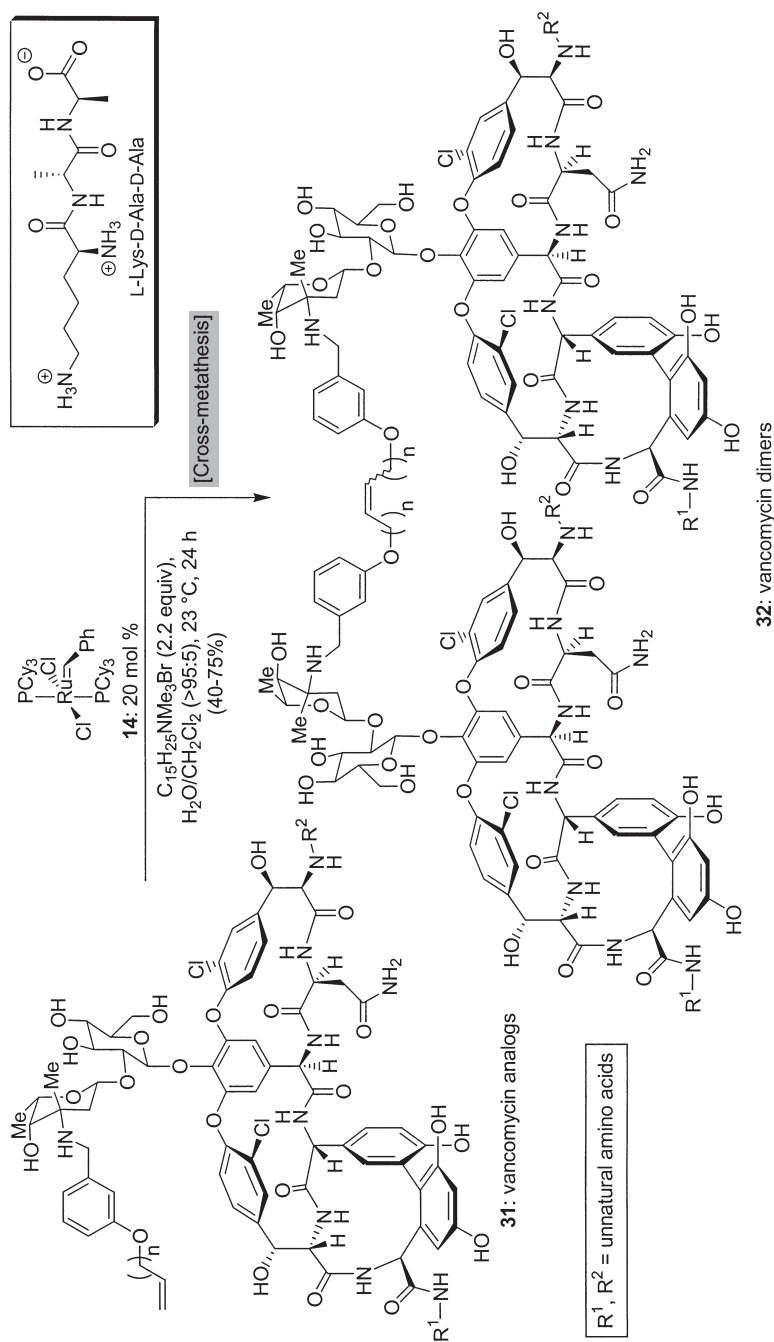


Scheme A.1-4. Ring-closing metathesis to fashion the B- and C-ring carbohydrates of an everninomicin A₁B(A)C model system (**30**).

plification to this new goal structure, the connection of these ring systems to metathesis became readily apparent. As shown in Scheme A.1-4, the use of this metathesis-based strategy ultimately proved fruitful as the complete A₁B(A)C assembly (**30**) of **24** was synthesized following the transformation of α,ω -diene **25** to **26** with ruthenium alkylidene **14**. Granting that this ring-closing reaction is far less groundbreaking than that effected in the context of the epothilones, the use of metathesis in this situation engendered a particularly concise entry to this complex natural product that would have been challenging to achieve otherwise with equal efficiency [16].

Metathesis applications in synthetic chemistry, however, go far beyond ring closures. Indeed, for many years numerous researchers have attempted to effect cross-metatheses between different olefin-containing substrates to generate new acyclic alkenes, thereby providing a transformation that might compete with more conventional approaches to access these compounds such as Wittig olefination. While some advances have been made, mixtures of products (often with uncontrolled stereochemistries) typically result due to competitive homodimerization (i.e., self-metathesis), since one of the reacting olefins is likely to exhibit greater reactivity than its partner [17]. Although future investigations may lead to the more reliable and predictable formation of such cross-products, the ease with which the dimerization of monomeric olefins can be achieved by metathesis is a notably convenient reaction which can be employed to access medicinally relevant compounds. Indeed, during the past decade several clinically employed compounds have been dimerized based on the notion that their biological activity will be enhanced [18]. Beyond this beneficial feature, dimerization can, in principle, afford a means to combat resistance developed to a particular drug by providing a new ligand predicated on a similar mode of action as the original agent, but which the bacterial/cellular machinery has not yet evolved to circumvent.

Our contributions to this burgeoning area of research have focused primarily on attempts to overcome bacterial resistance to vancomycin, the antibiotic currently considered as the last line of defense against methicillin-resistant *Staphylococcus aureus*, by using metathesis to dimerize vancomycin-like monomers such as **31** (Scheme A.1-5) to compounds of type **32** [19, 20]. Among several of the particularly noteworthy features of the developed cross-metathesis protocol to reach these agents (**32**) was the employment of a phase-transfer reagent (C₁₅H₂₅NMe₃Br) to encapsulate the ruthenium catalyst **14** and enable it to carry out its function effectively in aqueous media at 23 °C. Because these reaction parameters essentially are ambient conditions, it was then decided to extend this initial homodimerization approach to include the selective formation of heterodimers by adding combinations of different substrates of type **31** in the presence of vancomycin's biological target, a terminal L-Lys-D-Ala-D-Ala peptide subunit [20]. Since it had already been established that two monomers of vancomycin could bind simultaneously (and reversibly) to this target through separate hydrogen bonding networks [21], this design assumed that those monomers within the collection of examined substrates that bound most tightly to this peptide chain would be captured by cross-metathesis as a new dimer. As such, this approach should lead to the formation



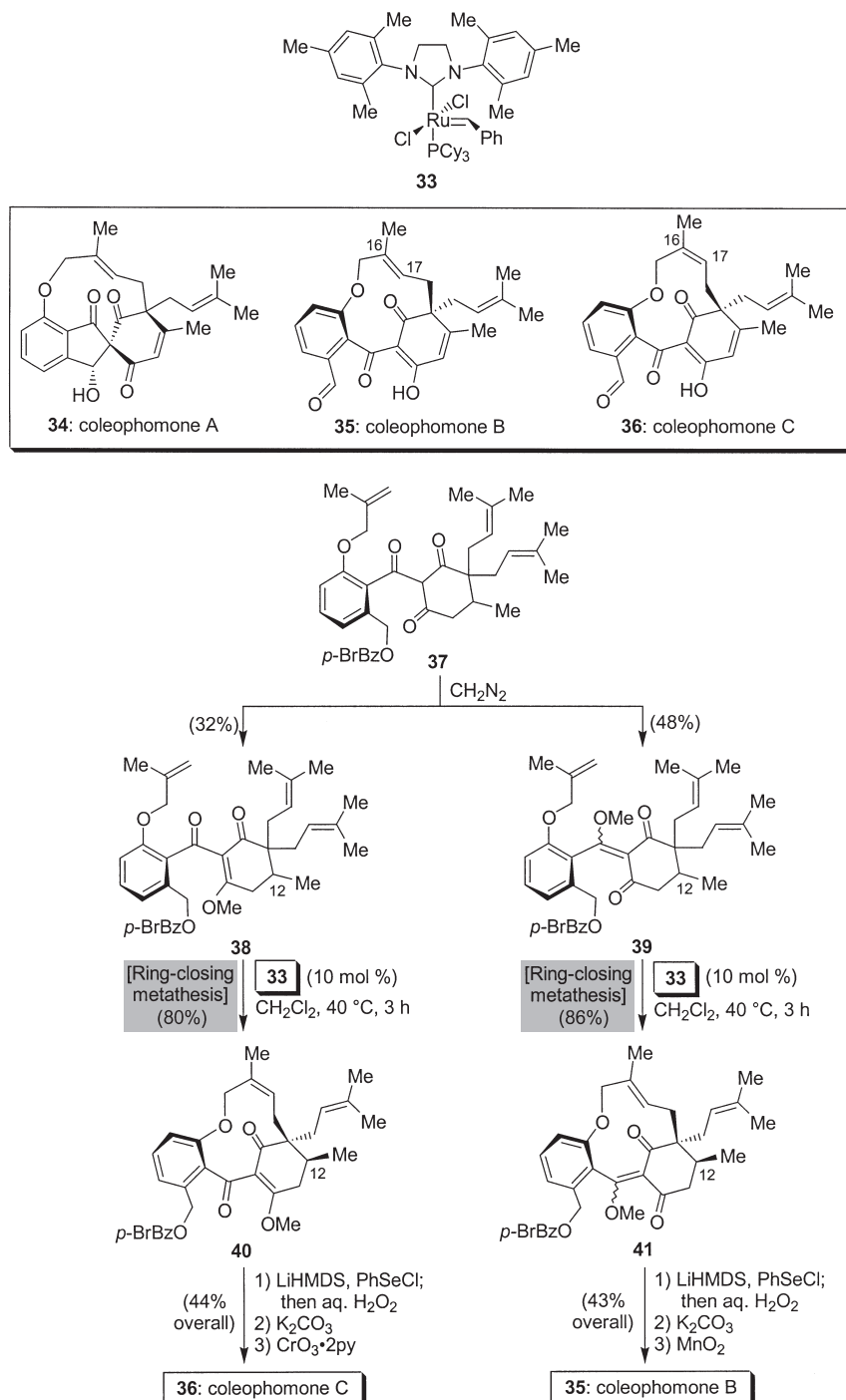
Scheme A.1-5. Dynamic combinatorial synthesis: the use of cross-metathesis to effect the formation of vancomycin dimers (32) under ambient-like conditions in the presence of its biological target, L-Lys-D-Ala-D-Ala.

of highly active antibacterial agents. Upon execution of this target-accelerated combinatorial strategy, also referred to as dynamic combinatorial screening [22], non-statistical distributions of dimers were formed. In each case the compound with the greatest potency (based on synthesizing and testing all potential dimers separately) was the predominant product in each round of compound formation. Significantly, several of the cross-metathesized agents prepared in this fashion demonstrated not only enhanced activity relative to vancomycin, but also potency against several, vancomycin-resistant bacterial strains.

With the development of new catalysts possessing unique reactivity profiles, however, comes the opportunity for groundbreaking applications of metathesis to generate even more complex molecular frameworks. For example, the recent disclosure of a novel family of ruthenium alkylidenes bearing structures such as **33** (Scheme A.1-6) has proven particularly useful in extending the frontiers of metathesis by enabling the successful realization of creative synthetic designs using reactions that would not have been possible with previously available catalysts [23]. Our final entry for this vignette, in which we sought to utilize metathesis as the key macrocycle-generating process to access members of the coleophomone family of natural products (**34–36**, Scheme A.1-6) [24], should serve to illustrate this point.

Our initial emphasis in this research program was to develop viable synthetic routes to coleophomones B (**35**) and C (**36**), natural products whose synthetically challenging architectures differ only in the geometry of their C16–C17 double bonds. While such macrocyclic alkenes clearly implicate the possibility of utilizing metathesis to fashion these ring junctions, the coleophomone context would appear to provide a fairly stringent test of available metathesis initiators. Indeed, literature precedent for forming 11-membered rings through this reaction was rather sparse [25], with none of the demonstrated examples providing a probe of the structural rigidity or potential stereoisomerism equivalent to that offered by the coleophomone structures. More importantly, this strategy would require the formation of a trisubstituted olefin, a structural motif that had proven virtually impossible to generate in macrocyclic systems with early ruthenium catalysts such as **14**. Even if the reaction itself could prove feasible, the most significant issue clouding the strategy was the stereoselectivity of the process, which could hardly be anticipated, but clearly stood as a critical element in reaching both **35** and **36**. Based on the epothilone studies where mixtures of geometrical isomers were typically obtained following ring closure, however, it seemed reasonable to presume that both geometrical isomers of the coleophomone macrocycle could be formed during a single metathesis event in the late stages of the synthesis, thereby providing a convergent pathway that would lead to both natural products. As it turned out, though, initial probes of the ring-closing metathesis event in several model systems indicated that such an assumption was incorrect, but that both isomers could be obtained in their pure geometrical formats in separate metathesis reactions simply through subtle modification of a single advanced intermediate.

The final strategy toward these natural products is shown in Scheme A.1-6. As indicated, after a convergent synthesis of **37** had been achieved, the somewhat



Scheme A.1-6. Application of the olefin metathesis reaction to the total synthesis of coleophomones B (**35**) and C (**36**).

labile tricarbonyl moiety in this intermediate was “protected” via methylation of the enol tautomers with CH_2N_2 . Although this step was nonselective, leading to the formation of both **38** and **39** differing only in the site in which a methyl group was incorporated, this result proved critical to the success of the overall approach. Separate exposure of **38** and **39** to a 10 mol % loading of catalyst **33** in CH_2Cl_2 for 3 hours effected the desired metathesis to the desired 11-membered macrocyclic system, but as a singular (and different) geometrical isomer in high yield based on the starting material employed. A few cursory modifications then provided the natural products from these advanced intermediates. While explanations for the stereoselectivity observed in these metathesis reactions are the subject of ongoing investigations, initial data suggest that both **40** and **41** reflect the kinetic product from their respective ring-closing processes as evidenced by the absence of any spiro-cyclopentene products (which should be thermodynamically more stable than a highly strained 11-membered ring) and *Z:E* mixtures. The overall diastereoselectivity of these ring-closing metatheses is particularly remarkable considering that only the prenyl group occupying the position *cis* to the adjacent methyl group at C-12 participated in each ring-closure. In hindsight, however, this outcome is reasonable in light of the fact that such a reactive conformation would place the remaining prenyl group *trans* to the C-12 methyl group, an arrangement that would correspond to the favored equatorial conformation for both groups on this cyclohexane ring.

While this example closes this account of our work on the olefin metathesis reaction as a tool for complex molecule construction [26], the emergence of additional applications of the process in organic synthesis is far from concluded. As new catalysts continue to exhibit improved levels of reactivity and selectivity, there is little doubt synthetic chemists will increasingly embrace this transformation as a standard method in their strategies for complex molecule construction [27]. To be sure, many more amazing applications of metathesis reactions will be reported as we move further into the 21st century. Ironically, although the ultimate goal of synthetic chemistry is to mimic nature in her efficiency to synthesize organic molecules, through the olefin metathesis reaction we now have a tool that takes us closer to that goal for which nature herself has no direct rival that we know of today.

Acknowledgments

It is with enormous pride and pleasure that we wish to thank the members of the group who contributed to the syntheses presented in this account and made the described chemistry both possible and enjoyable. Financial support for this work was provided by the National Institutes of Health (USA), the Skaggs Institute for Chemical Biology, pre-doctoral fellowships from the National Science Foundation and Pfizer (S.A.S.), and grants from Merck & Co., DuPont, Schering Plough, Hoffmann-LaRoche, GlaxoWellcome, Rhone-Poulenc Rorer, Amgen, Novartis, Abbott Laboratories, Bristol-Myers Squibb, Boehringer Ingelheim, Zeneca, American BioScience, CaPCURE, and the George E. Hewitt Foundation.

References

- 1 O. DIELS, K. ALDER, *Annalen* **1928**, 460, 98. For a review of this reaction in total synthesis, see: K. C. NICOLAOU, S. A. SNYDER, T. MONTAGNON, G. E. VASSILIKOGIANNAKIS, *Angew. Chem.* **2002**, 114, 1742; *Angew. Chem. Int. Ed.* **2002**, 41, 1668.
- 2 G. WITTIG, G. GEISSLER, *Liebigs Ann.* **1953**, 580, 44. For a review of this reaction in total synthesis, see: K. C. NICOLAOU, M. W. HÄRTER, J. L. GUNZNER, A. NADIN, *Liebigs Ann.* **1997**, 1283.
- 3 The origin of olefin metathesis occurred several decades earlier. For some reviews of the early history of olefin metathesis, see: a) T. J. KATZ, *Advan. Organomet. Chem.* **1977**, 16, 283; b) R. H. GRUBBS, *Prog. Inorg. Chem.* **1978**, 24, 1; c) R. H. GRUBBS, W. TUMAS, *Science* **1989**, 243, 907.
- 4 Critical in this regard were studies toward Sch38516 and manzamine A: a) A. F. HOURI, Z. XU, D. A. COGAN, A. H. HOVEYDA, *J. Am. Chem. Soc.* **1995**, 117, 2943; b) S. F. MARTIN, Y. LIAO, Y. WONG, T. REIN, *Tetrahedron Lett.* **1994**, 35, 691; c) B. C. BORER, S. DEERENBERG, H. BIERAUGEL, U. K. PANDIT, *Tetrahedron Lett.* **1994**, 35, 3191.
- 5 a) K. C. NICOLAOU, M. H. D. POSTEMA, C. F. CLAIBORNE, *J. Am. Chem. Soc.* **1996**, 118, 1565; b) K. C. NICOLAOU, M. H. D. POSTEMA, E. W. YUE, A. NADIN, *J. Am. Chem. Soc.* **1996**, 118, 10335.
- 6 a) F. N. TEBBE, G. W. PARSHALL, G. S. REDDY, *J. Am. Chem. Soc.* **1978**, 100, 3611; b) F. N. TEBBE, G. W. PARSHALL, D. W. OVENALL, *J. Am. Chem. Soc.* **1979**, 101, 5074.
- 7 For a more recent application of olefin metathesis to form polyethers using a ROM/RCM sequence, see: K. C. NICOLAOU, J. A. VEGA, G. VASSILIKOGIANNAKIS, *Angew. Chem.* **2001**, 113, 4573; *Angew. Chem. Int. Ed.* **2001**, 40, 4441.
- 8 For some recent reviews of this expanding area of research, see: a) K. C. NICOLAOU, A. RITZÉN, K. NAMOTO, *Chem. Commun.* **2001**, 1523; b) K. C. NICOLAOU, F. ROSCHANGAR, D. VOURLOUMIS, *Angew. Chem.* **1998**, 110, 2120; *Angew. Chem. Int. Ed.* **1998**, 37, 2014.
- 9 G. C. FU, S. T. NGUYEN, R. H. GRUBBS, *J. Am. Chem. Soc.* **1993**, 115, 9856. For a later example employing a free alcohol in a complex molecule synthesis, see: M. T. CRIMMINS, B. W. KING, *J. Org. Chem.* **1996**, 61, 4192.
- 10 a) P. SCHWAB, M. B. FRANCE, J. W. ZILLER, R. H. GRUBBS, *Angew. Chem.* **1995**, 107, 2179; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2039; b) P. SCHWAB, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1996**, 118, 100.
- 11 Z. YANG, Y. HE, D. VOURLOUMIS, H. VALLBERG, K. C. NICOLAOU, *Angew. Chem.* **1997**, 109, 170; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 166. For earlier model studies, see: K. C. NICOLAOU, Y. HE, D. VOURLOUMIS, H. VALLBERG, Z. YANG, *Angew. Chem.* **1996**, 108, 2554; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2399. For the full account of this work, see: K. C. NICOLAOU, Y. HE, D. VOURLOUMIS, H. VALLBERG, F. ROSCHANGAR, F. SARABIA, S. NINKOVIC, Z. YANG, J. I. TRUJILLO, *J. Am. Chem. Soc.* **1997**, 119, 7960.
- 12 For examples and discussion of this concept, see A. FÜRSTNER, T. DIERKES, O. R. THIEL, G. BLANDA, *Chem. Eur. J.* **2001**, 7, 5286 and references cited therein.
- 13 For general discussions of this topic, see: *Handbook of Combinatorial Chemistry: Drugs, Catalysts, Methods*, Vols. 1 & 2 (Eds.: K. C. NICOLAOU, R. HANKO, W. HARTWIG), Wiley-VCH, Weinheim, **2002** p. 1114.
- 14 a) K. C. NICOLAOU, N. WINSSINGER, J. PASTOR, S. NINKOVIC, F. SARABIA, D. VOURLOUMIS, Z. YANG, T. LI, P. GIANNAKAKOU, E. HAMEL, *Nature* **1997**, 387, 268; b) K. C. NICOLAOU, D. VOURLOUMIS, T. LI, J. PASTOR, N. WINSSINGER, Y. HE, S. NINKOVIC, F. SARABIA, H. VALLBERG, F. ROSCHANGAR, N. P. KING, M. R. V. FINLAY, P. GIANNAKAKOU, P. VERDIER-PINARD, E. HAMEL, *Angew. Chem.*

- 1997, 109, 2181; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2097. For additional library construction by parallel solution-phase synthesis, see: K. C. NICOLAOU, H. VALLBERG, N. P. KING, F. ROSCHANGAR, Y. HE, D. VOURLUMIS, C. G. NICOLAOU, *Chem. Eur. J.* **1997**, 3, 1957.
- 15 K. C. NICOLAOU, R. M. RODRÍGUEZ, H. J. MITCHELL, F. L. VAN DELFT, *Angew. Chem.* **1998**, 110, 1975; *Angew. Chem. Int. Ed.* **1998**, 37, 1874.
- 16 For the eventual total synthesis of this complex oligosaccharide, see: a) K. C. NICOLAOU, R. M. RODRÍGUEZ, H. J. MITCHELL, H. SUZUKI, K. C. FYLAKTAKIDOU, O. BAUDOUIN, F. L. VAN DELFT, *Chem. Eur. J.* **2000**, 6, 3095; b) K. C. NICOLAOU, H. J. MITCHELL, K. C. FYLAKTAKIDOU, R. M. RODRÍGUEZ, H. SUZUKI, *Chem. Eur. J.* **2000**, 6, 3116; c) K. C. NICOLAOU, H. J. MITCHELL, K. C. FYLAKTAKIDOU, R. M. RODRÍGUEZ, H. SUZUKI, S. R. CONLEY, *Chem. Eur. J.* **2000**, 6, 3149.
- 17 General discussion of this topic can be found in the following recent reviews: a) T. M. TRNKA, R. H. GRUBBS, *Acc. Chem. Res.* **2001**, 34, 18; b) A. FÜRSTNER, *Angew. Chem.* **2000**, 112, 3140; *Angew. Chem. Int. Ed.* **2000**, 39, 3012; c) R. H. GRUBBS, S. CHANG, *Tetrahedron* **1998**, 54, 4413; d) M. SCHUSTER, S. BLECHERT, *Angew. Chem.* **1997**, 109, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2036.
- 18 For representative references, see: a) J. P. MACKAY, U. GERHARD, D. A. BEAUREGARD, R. A. MAPLESTONE, D. H. WILLIAMS, *J. Am. Chem. Soc.* **1994**, 116, 4573; b) P. J. LOIL, A. E. BEVIVINO, B. D. KORTY, P. H. AXELSEN, *J. Am. Chem. Soc.* **1997**, 119, 1516; c) T. STAROSKE, D. P. O'BRIEN, T. J. D. JORGENSEN, P. ROEPSTORFF, D. H. WILLIAMS, A. J. R. HECK, *Chem. Eur. J.* **2000**, 6, 504; d) S. J. SUCHECK, A. L. WONG, K. M. KOELLER, D. D. BOEHR, K. DRAKER, P. SEARS, G. D. WRIGHT, C.-H. WONG, *J. Am. Chem. Soc.* **2000**, 122, 5230; e) D. BRADLEY, *Drug Discovery Today* **2000**, 5, 44; f) M. M. MAMMEN, S.-K. CHOI, G. M. WHITESIDES, *Angew. Chem.* **1998**, 110, 2908; *Angew. Chem. Int. Ed.* **1998**, 37, 2754.
- 19 For reviews on vancomycin, see: a) K. C. NICOLAOU, C. N. C. BODDY, S. BRÄSE, N. WINSSINGER, *Angew. Chem.* **1999**, 112, 2230; *Angew. Chem. Int. Ed.* **1999**, 38, 2096; b) K. C. NICOLAOU, C. N. C. BODDY, *Sci. Am.* **2001**, 284, 46.
- 20 a) K. C. NICOLAOU, S. Y. CHO, R. HUGHES, N. WINSSINGER, C. SMETHURST, H. LABISCHINSKI, R. ENDERMANN, *Chem. Eur. J.* **2001**, 7, 3798; b) K. C. NICOLAOU, R. HUGHES, S. Y. CHO, N. WINSSINGER, H. LABISCHINSKI, R. ENDERMANN, *Chem. Eur. J.* **2001**, 7, 3824.
- 21 a) D. H. WILLIAMS, A. J. MAGUIRE, W. TSUZUKI, M. S. WESTALL, *Science* **1998**, 280, 711; b) U. GERHARD, J. P. MACKAY, R. A. MAPLESTONE, D. H. WILLIAMS, *J. Am. Chem. Soc.* **1993**, 115, 232; c) J. P. MACKAY, U. GERHARD, D. A. BEAUREGARD, M. S. WESTALL, M. S. SEARLE, D. H. WILLIAMS, *J. Am. Chem. Soc.* **1994**, 116, 4851.
- 22 For an entry to this field, see the following papers and references cited therein: a) J.-M. LEHN, A. V. ELISEEV, *Science* **2001**, 291, 2331; b) G. R. L. COUSINS, R. L. E. FURLAN, Y.-F. NG, J. E. REDMAN, J. K. M. SANDERS, *Angew. Chem.* **2001**, 113, 437; *Angew. Chem. Int. Ed.* **2001**, 40, 423; c) J. P. NAWROCKI, M. WIGGER, S. AUDELAT, S. A. BENNER, *Synlett* **1998**, 688; d) H. HOIKI, W. C. STILL, *J. Org. Chem.* **1998**, 63, 904.
- 23 a) M. SCHOLL, S. DING, C. W. LEE, R. H. GRUBBS, *Org. Lett.* **1999**, 1, 953; b) M. SCHOLL, T. M. TRNKA, J. P. MORGAN, R. H. GRUBBS, *Tetrahedron Lett.* **1999**, 40, 2247. For related studies with similar ligands concurrent to this work, see: c) J. K. HUANG, E. D. STEVENS, S. P. NOLAN, J. L. PETERSEN, *J. Am. Chem. Soc.* **1999**, 121, 2674; d) L. ACKERMANN, A. FÜRSTNER, T. WESKAMP, F. J. KOHL, W. A. HERRMANN, *Tetrahedron Lett.* **1999**, 40, 4787.
- 24 K. C. NICOLAOU, G. E. VASSILIKOGIANNAKIS, T. MONTAGNON, *Angew. Chem.* **2002**, 114, 3410; *Angew. Chem. Int. Ed.* **2002**, 41, 3276.

- 25 a) H. EL SUKKARI, J.-P. GESSON, B. RENOUX, *Tetrahedron Lett.* **1998**, 39, 4043; b) J. D. WINKLER, J. M. HOLLAND, J. KASPAREC, P. H. AXELSEN, *Tetrahedron* **1999**, 55, 8199; c) T. R. HOYE, M. A. PROMO, *Tetrahedron Lett.* **1999**, 40, 1429; d) M. ARISAWA, C. KATO, H. KANEKO, A. NISHIDA, M. NAKAGAWA, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1873.
- 26 For general reviews of some of the syntheses discussed in this vignette as well as others from this group, see: a) K. C. NICOLAOU, D. VOURLOUMIS, N. WINSSINGER, P. S. BARAN, *Angew. Chem.* **2000**, 112, 46; *Angew. Chem. Int. Ed.* **2000**, 39, 44; b) K. C. NICOLAOU, H. J. MITCHELL, *Angew. Chem.* **2001**, 113, 1624; *Angew. Chem. Int. Ed.* **2001**, 40, 1576.
- 27 To be sure, this trend is already evident as a search on SciFinder Scholar at the end of July 2002 using the key words “total synthesis” and “olefin metathesis” in combination revealed close to 75 hits in the primary literature, the vast majority of which were from the last three to four years.

2.9 Vignette 2

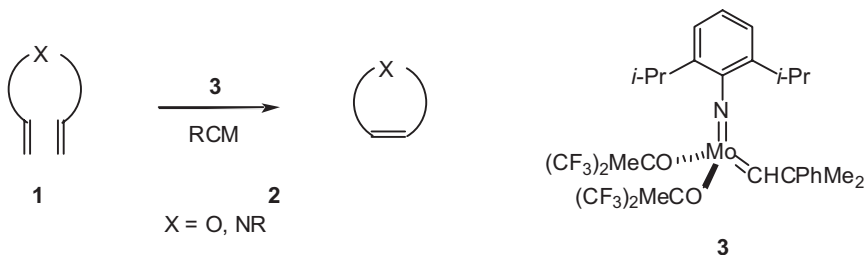
Applications of Ring-Closing Metathesis to Alkaloid Synthesis

Stephen F. Martin

Introduction

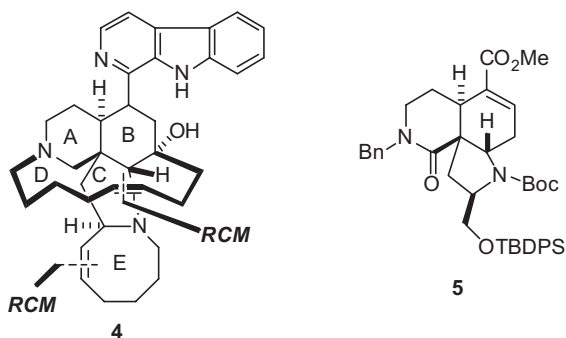
From time to time an article appears in the chemical literature that has immediate relevance to solving a significant problem that is subject to current investigation in one's own laboratory. Such was the case in 1992 when Grubbs and Fu published two papers in quick succession describing the application of ring-closing metathesis (RCM) to the syntheses of simple 5-, 6-, and 7-membered monocyclic systems containing oxygen and nitrogen atoms (Scheme A.2-1) [1]. The highly active and commercially available Schrock molybdenum catalyst **3** [2] had been found to have reasonable functional group tolerance and was employed to induce these cyclizations. Although olefin metathesis and RCM were certainly not new reactions [3], these seminal papers revealed for the first time that the RCM of α,ω -dienes with an oxygen or nitrogen atom in the tether linking the two olefinic moieties could be used in a practical manner to construct a variety of oxygen and nitrogen heterocycles. Shortly after these reports, Forbes used the same catalyst to prepare unsaturated carbocycles by RCM [4]. An exciting new way to create heterocycles and carbocycles had thus emerged, and the age of RCM as an important tool for organic synthesis had dawned.

At the time the Grubbs and Fu papers appeared in 1992, we were involved in the synthesis of the structurally complex anticancer alkaloid manzamine A (**4**) [5]. In particular, we were faced with the considerable challenge of annelating the



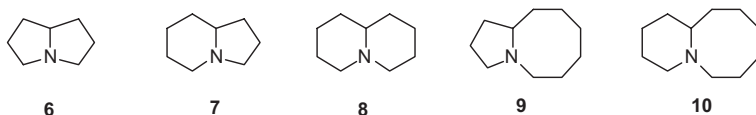
Scheme A.2-1

8-membered E-ring onto a preexisting ABC ring core derived from **5**, which was then in hand. We had been considering the relative virtues of using intramolecular Wittig reactions or McMurry couplings for this purpose, but we were immediately attracted to the more exciting possibility of exploiting RCM to form the E-ring. We were aware of the potential pitfalls associated with constructing an 8-membered ring via RCM, especially since there were no such examples in the literature. However, we believed that conformational constraints enforced by the presence of the C-ring would facilitate the desired cyclization, even though there was no precedent to justify such optimism. We were of course mindful that RCM might also be used to elaborate the 13-membered D-ring.

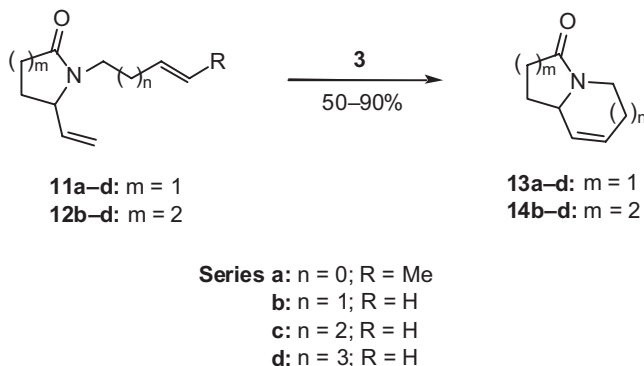


Methodological Studies

Synthesis of fused bicyclic nitrogen heterocycles RCM as a method for ring construction captured our attention because of our work directed toward manzamine A. However, our long-standing interest in alkaloid synthesis prompted us to initiate a series of simple model studies to assess more generally the feasibility of forming azabicyclic ring systems such as **6–10** by RCM. These heterocycles occur in a large number of alkaloid natural products; therefore, the ability to develop a new entry to these ring systems might be expected to have a significant impact on alkaloid synthesis.

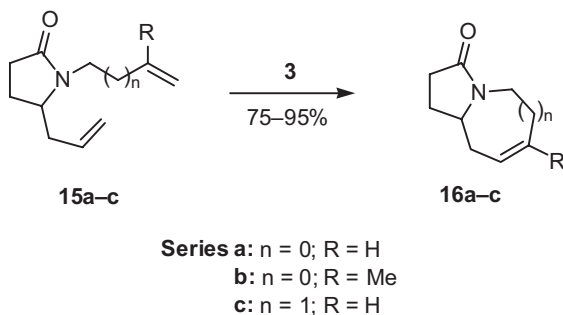


We first prepared the diene **11d** and discovered that it underwent a facile RCM in the presence of the Schrock catalyst **3** to give the pyrrolidinoazocine **13d** in about 50% yield (Scheme A.2-2). This initial result was significant because it validated the potential of using a RCM reaction to form the 8-membered E-ring of manzamine A. The α,ω -dienes **11a–c**, **12b–d**, and **15a–c** were then prepared, and these were also found to undergo facile RCM cyclizations in the presence of the



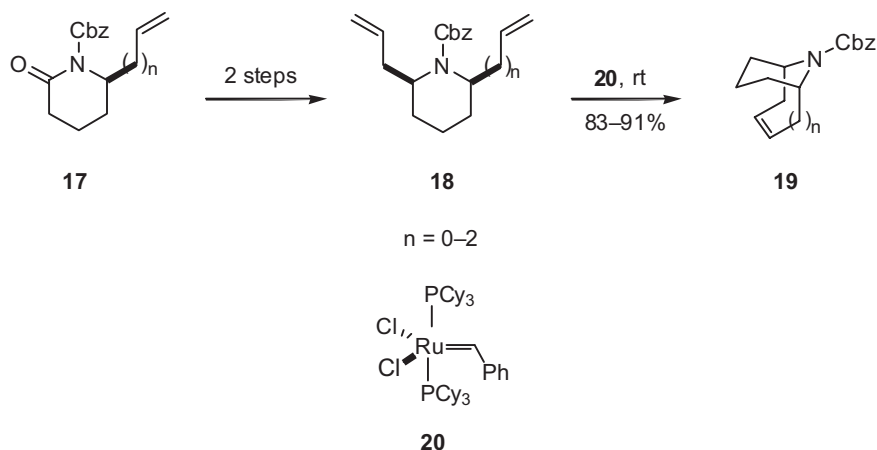
Scheme A.2-2

Schrock catalyst **3** to give the corresponding bicyclic systems **13a–d**, **14b–d**, and **15a–c** (Schemes A.2-2 and A.2-3) [6]. Although these reactions were typically not optimized, they usually proceeded in good yields. These results thus signaled that RCM could be used to form a variety of fused nitrogen heterocycles in addition to the monocyclic systems reported by Grubbs and Fu [1b].



Scheme A.2-3

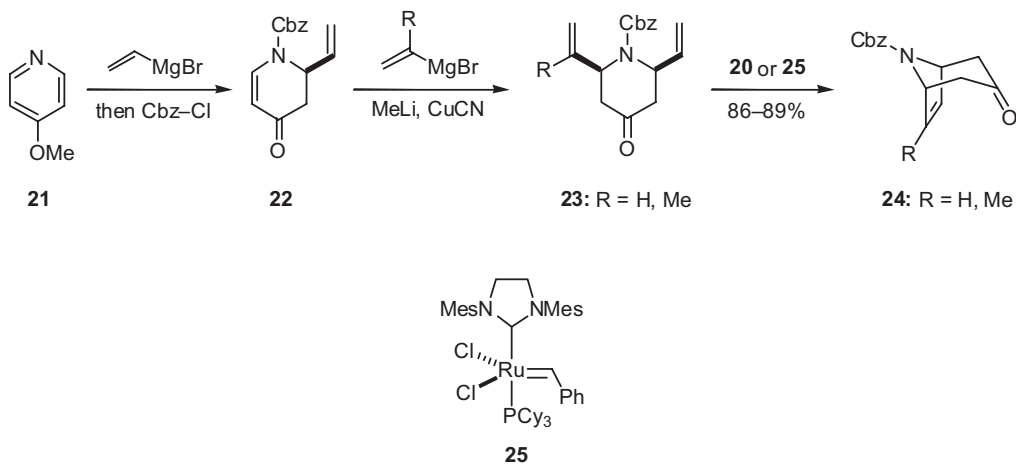
Synthesis of bridged bicyclic nitrogen heterocycles A number of alkaloids possess a nitrogen atom in the one-atom bridge of a [n.3.1] bicyclic ring system, and therefore there has been a long-standing interest in developing new tactics for preparing such structural arrays. In this context, we recently discovered that RCM reactions may be utilized to provide facile access to a number of azabicyclo[n.3.1]alkenes [7]. For example, alkenyl-substituted 2-piperidone derivatives **17** ($n = 0–2$), which were prepared in four steps from glutarimide, were converted into the α,ω -dienes **18** by sequential hydride reduction and treatment with allyltrimethylsilane in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme A.2-4). The preferential formation of *cis*-2,6-dialkenyl piperidines **18** arises from a combination of $A^{1,3}$ -strain in the intermediate *N*-acyl iminium ion and stereoelectronic control in the nucleophilic addition of allyltrimethylsilane to this ion [8]. Significantly, $A^{1,3}$ -strain in **18** was also expected to favor an axial orientation for each of the alkenyl side chains, thereby enforcing a



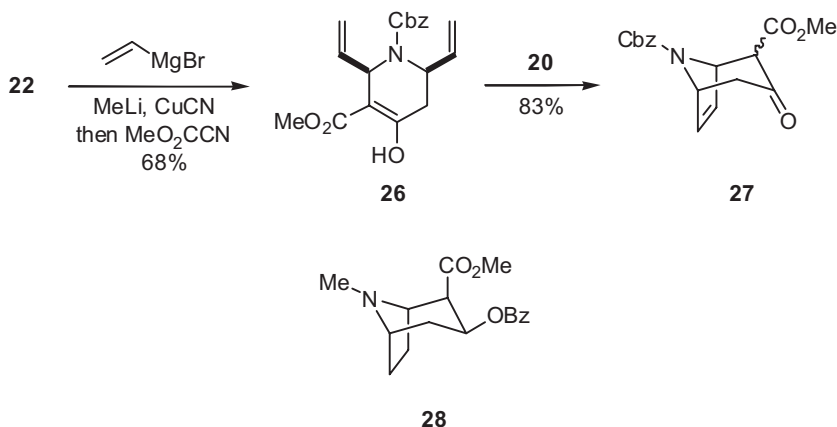
Scheme A.2-4

conformational bias on the system that was required for cyclization via RCM. Indeed, exposure of **18** ($n = 0-2$) to the Grubbs catalyst **20** led to the rapid formation of the corresponding bridged bicyclic product **19** ($n = 0-2$) in excellent yields.

Of the bridged bicyclic systems that occur in alkaloids, the tropane skeleton is perhaps the most important. Construction of this ring system requires the availability of *cis*-2,6-divinyl piperidines, and we encountered some difficulties in preparing such compounds stereoselectively and efficiently from **17** ($n = 0$). We therefore developed a stereoselective approach to the related 4-piperidinone derivatives **23** ($R = \text{H}, \text{Me}$) that was inspired by the work of Comins (Scheme A.2.5) [7, 9]. Although **23** ($R = \text{H}$) underwent a facile RCM in the presence of **20** to give the tropane derivative **24** ($R = \text{H}$), the more reactive “second-generation” Grubbs catalyst **25** [10] was required to cyclize **23** ($R = \text{Me}$) to provide **24** ($R = \text{Me}$).



Scheme A.2-5

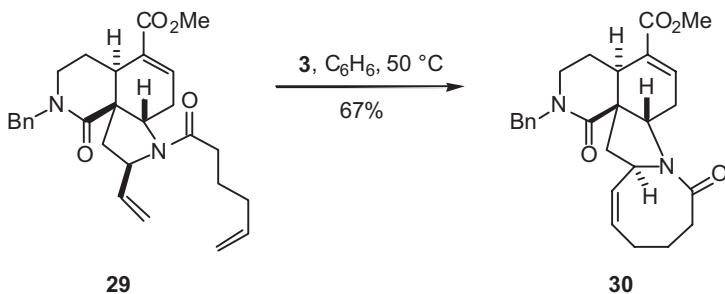


Scheme A.2-6

In order to exemplify the potential of this chemistry to the synthesis of the biologically important tropane alkaloids, the enolate obtained by addition of vinyl cuprate to **22** was trapped with methyl cyanoformate to provide **26** (Scheme A.2-6). Cyclization of **26** in the presence of **20** gave **27**, a potential precursor of cocaine (**28**) and related tropane alkaloids.

Synthesis of Alkaloid Natural Products

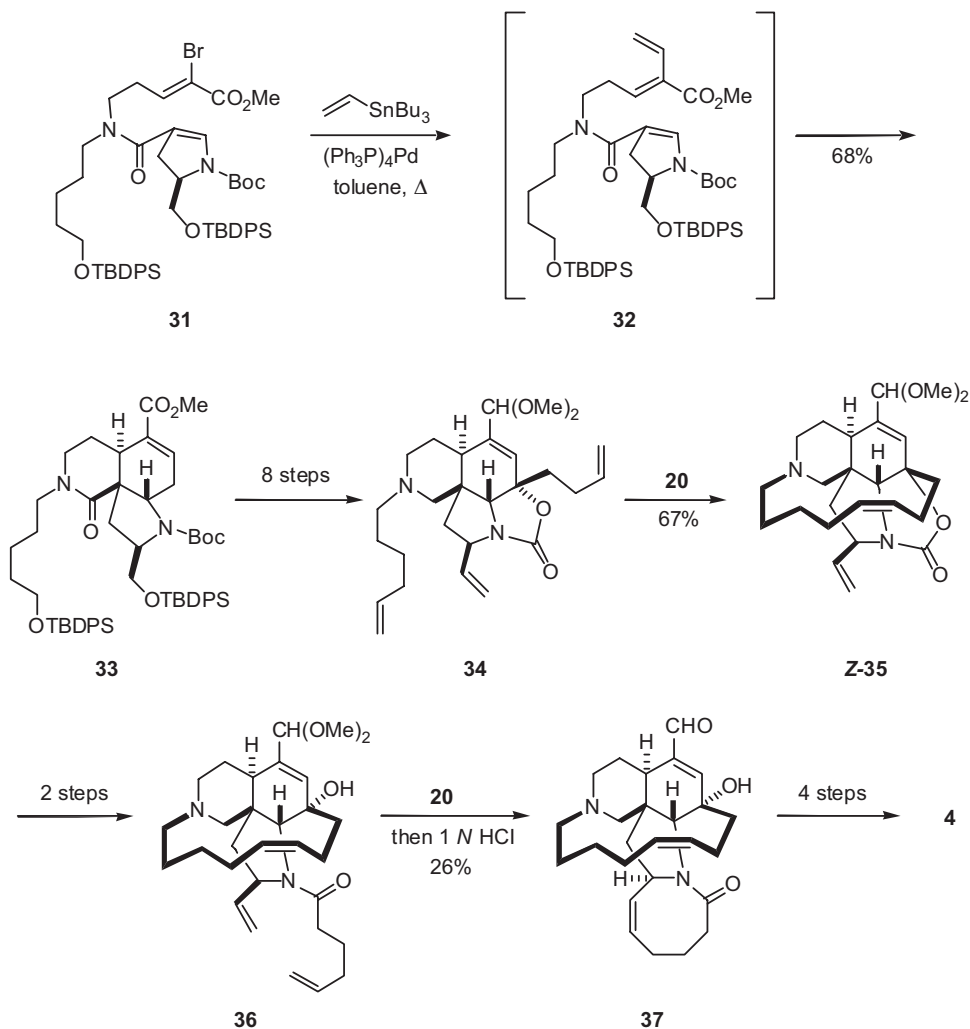
Total synthesis of manzamine A (4) The aforementioned model studies clearly established RCM as a useful tool for preparing nitrogen heterocycles possessing modest functional and structural complexity. However, the true test of any methodology lies in its applicability to solving practical problems that are typically encountered in the context of synthesizing desired target molecules. As noted previously, our original interest in RCM was inspired by its possible application to the synthesis of manzamine A (**4**). We thus turned our attention toward evaluating whether RCM might be used to annelate an 8-membered ring onto the putative manzamine A precursor **5**. Toward this end, **5** was converted in five simple operations into **29** (Scheme A.2-7) [11]. When **29** was heated in the presence of the



Scheme A.2-7

Schrock catalyst **3**, smooth cyclization ensued to deliver **30** in good yield. The promise of RCM reactions in the context of preparing complex and highly functionalized natural products was then evident.

Although we considered using **30** as an intermediate in the synthesis of manzamine A, a more streamlined approach to this natural product was ultimately developed that featured forming both the fused 8-membered ring and the bridged 13-membered ring by RCM reactions. The highlights of this synthesis, which was some years in its development, are summarized in Scheme A.2-8 [12]. The tricyclic intermediate **33** was assembled from **31** by a novel domino Stille/Diels-Alder sequence in which three new carbon-carbon bonds were stereoselectively formed



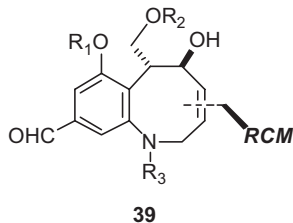
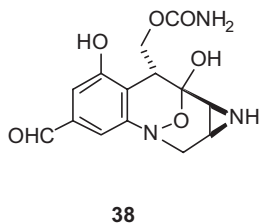
Scheme A.2-8

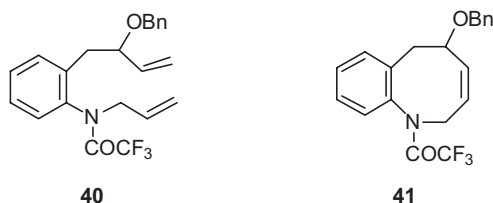
in a single operation. The stereochemistry of the intramolecular cycloaddition to give **33** was controlled by the lone stereocenter in **32** that arose from (*R*)-pyroglutamic acid.

The cycloadduct **33** was converted in eight steps into **34**, thereby setting the stage for the first RCM reaction to form the bridged 13-membered ring of manzamine A. In the event, heating **34** in the presence of the Grubbs ruthenium catalyst **20** [13] delivered a mixture of geometric isomers (*Z/E* = 8:1) from which *Z*-**35** was isolated in 67% yield [14]. The ease and efficiency of this cyclization is remarkable. Free tertiary amino groups may sometimes interfere with RCM reactions using **20** as catalyst [15]; however, protonation of the tertiary amine in **34** prior to inducing the RCM had no beneficial effect and was unnecessary. In marked contrast to the facility with which **34** underwent RCM, the cyclization of **36**, which was prepared in two steps from *Z*-**35**, proved far more difficult than anticipated based upon our prior experience with **29**. The yield of the RCM of **36** leading to **37** was only about 30%, even when high catalyst loadings of **20** were used or the more reactive **3** was employed as the catalyst. We examined this reaction in some detail but were unable to identify the source of the difficulty. Compound **37** was then transformed into manzamine A (**4**), thus completing an enantioselective synthesis of **4** that required only 26 chemical operations from commercially available starting materials [16].

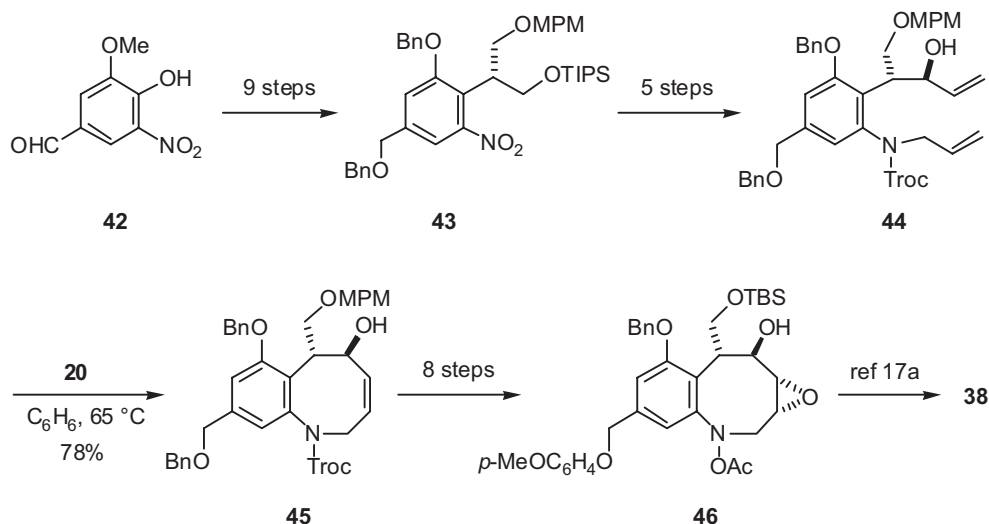
This synthesis of manzamine A represents one of the more complex settings in which RCM reactions have been applied. However, contemporaneous with these synthetic efforts, we were interested in further developing RCM reactions as a useful construct for alkaloid synthesis, and some of these successes are summarized in the following sections.

Formal synthesis of FR900482 (38) One target of interest was the anticancer agent FR900482 (**38**) that is related to the mitomycins and had been previously prepared in several different laboratories [17]. In our retrosynthetic analysis of **38**, we were attracted to the potential intermediacy of the benzoazocine **39**, which we reasoned would be readily accessible via an RCM reaction. Prior to embarking upon the synthesis of FR900482, we conducted a quick model study to test the feasibility of using RCM to form the benzoazocine ring system because we knew that forming 8-membered rings via such cyclizations could be problematic [18]. The diene **40** was thus prepared, and we discovered that it underwent facile RCM upon heating in the presence of the Schrock catalyst **3** to furnish **41** in 77% yield [19, 20].



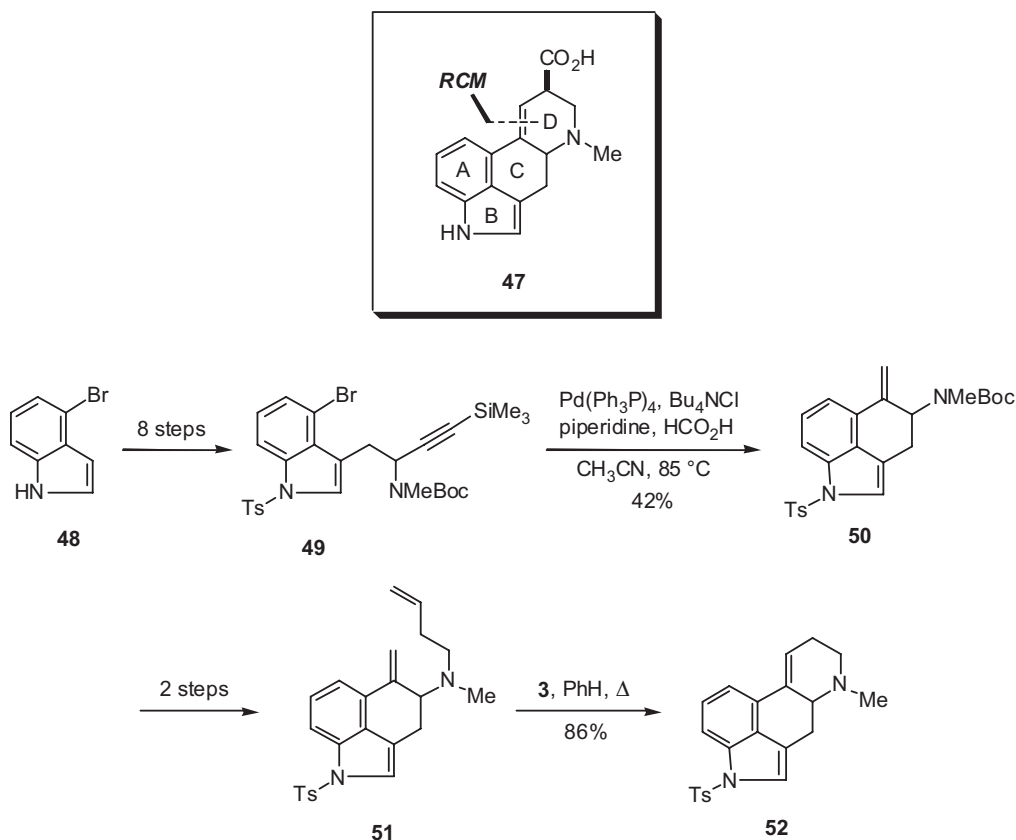


Thus armed with confidence in the key RCM reaction, we developed the successful approach to FR900482 (**38**) that is outlined in Scheme A.2-9 [21]. Commercially available **42** was converted into racemic **43** in nine steps, while an enantioselective synthesis of **43** from **42** required 11 steps. Stereoselective elaboration of **43** into **44** involved five steps and set the stage for the RCM. When a dilute solution of **44** in benzene was heated in the presence of the Grubbs catalyst **20**, the benzoazocine **45** was isolated in 78% yield. The subsequent transformation of **45** into **46**, which had been previously converted into FR900482 by Fukuyama [17a], then completed a formal synthesis of **38**.



Scheme A.2-9

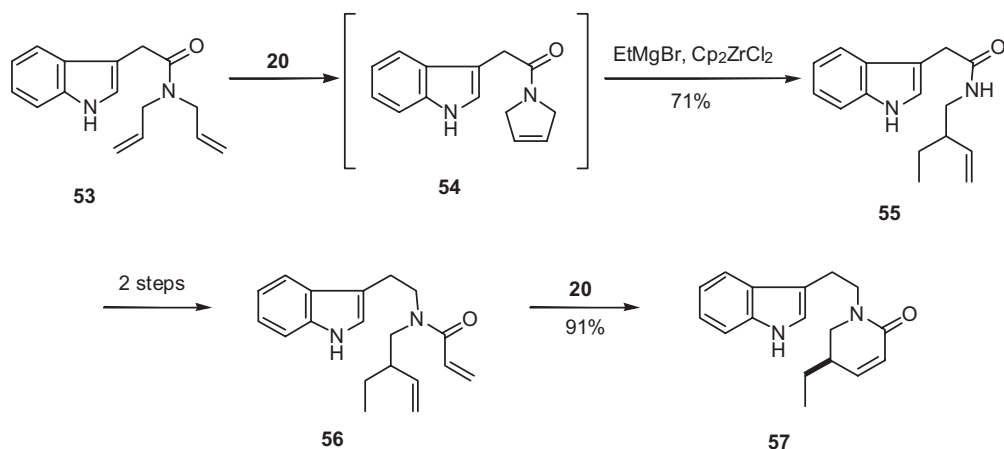
Approach to the Ergot alkaloids Lysergic acid (**47**) is an indole alkaloid that has a rich history in organic chemistry owing to a combination of its structure and the biological activity of some of its derivatives [22]. We have been interested in designing new strategies for the synthesis of **47** and related *Ergot* alkaloids for a number of years [23], and we became intrigued by the possibility of forming the D-ring via an RCM as a late step in a synthesis of lysergic acid (**47**). In order to explore the underlying feasibility of such an approach, readily available 4-bromoindole (**48**) was first transformed into **49**, which was then cyclized to **50** via a



Scheme A.2-10

regioselective Heck reaction (Scheme A.2-10) [24]. Removal of the *N*-Boc protecting group followed by *N*-alkylation gave **51**. Although **51** did not undergo significant RCM in the presence of the Grubbs catalyst **20**, the more reactive Schrock catalyst **3** induced the desired RCM to give **52** in excellent yield. This cyclization is noteworthy because there were relatively few examples of RCM reactions involving exocyclic olefins [25] or phenyl-substituted alkenes [26]. This model study validates our approach to the synthesis of lysergic acid, and work in this area is ongoing.

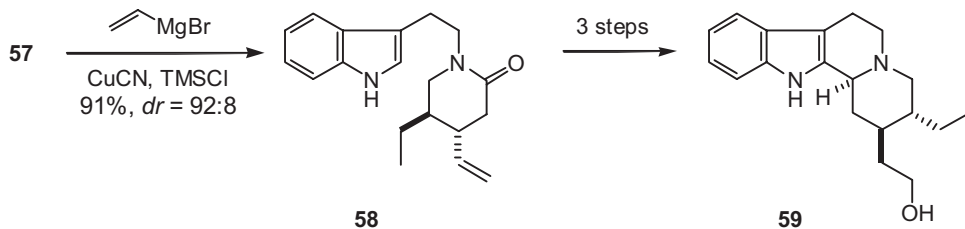
Synthesis of corynantheane and oxindole alkaloids In the context of developing general entries to various other classes of indole alkaloids, we envisioned that **57** might be a pivotal intermediate in the syntheses of a number of interesting targets. The utility of **57** would derive from the presence of an α,β -unsaturated lactam moiety that could serve as an acceptor in 1,4-additions with selected nucleophiles. The problem then was to design a concise route to **57**. After considering several possibilities, a novel approach was developed that features the RCM of the diallyl amide **53** using the Grubbs catalyst **20** to generate **54** as an unisolated interme-



Scheme A.2-11

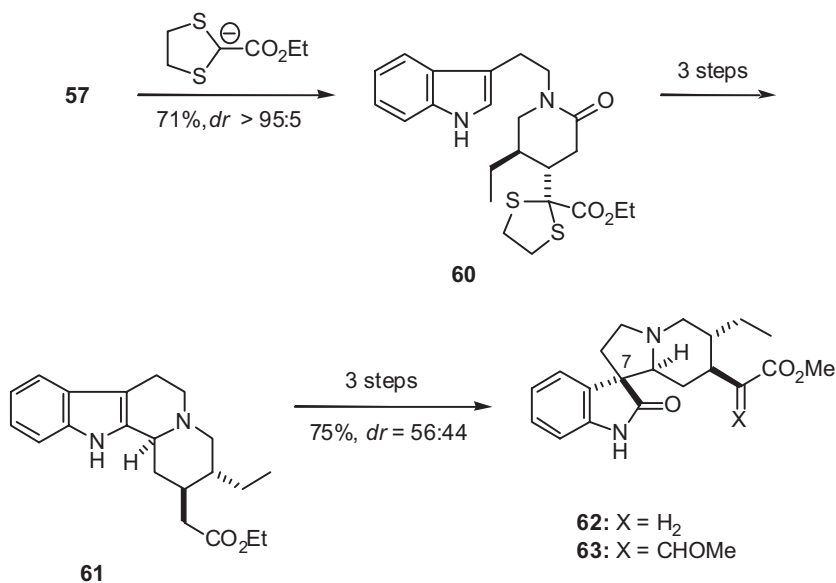
diolate that was subjected directly to a zirconocene-catalyzed carbomagnesation to deliver the homoallylic amine **55** (Scheme A.2-11) [27, 28]. It is perhaps noteworthy that the conversion of **53** into **55** represents the first use of a tandem RCM/carbomagnesation sequence in alkaloid synthesis. Compound **55** was then transformed into **56**, which underwent a second RCM reaction in the presence of **20** to give **57** in excellent yield.

The utility of **57** as a versatile intermediate was first demonstrated by its conversion into dihydrocorynantheol (**59**) (Scheme A.2-12). This synthesis commenced with the diastereoselective 1,4-addition of a vinyl cuprate to **57** to produce **58**. Subsequent cyclization of **58** via a Bischler-Napieralski reaction followed by hydride reduction and a hydroboration/oxidation completed a short synthesis of **59**.



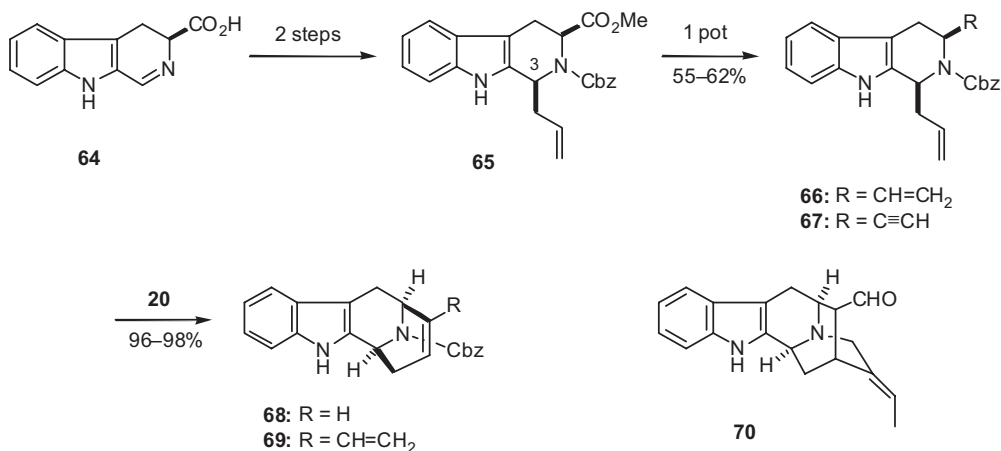
Scheme A.2-12

The lactam **57** was also employed as a precursor of the oxindole alkaloid rhynchophylline (**63**) (Scheme A.2-13). In the event, **57** underwent a highly stereoselective 1,4-addition of a dithiolane anion to give **60**, which was converted into **61** in three straightforward steps. As expected from prior art [29], the oxidative rearrangement of **61** furnished a separable mixture (ca 1.3:1) of **62** together with its C(7) epimer. Compound **62** had been converted into rhynchophylline by Ban [30] and its preparation therefore constituted a formal synthesis of **63**.

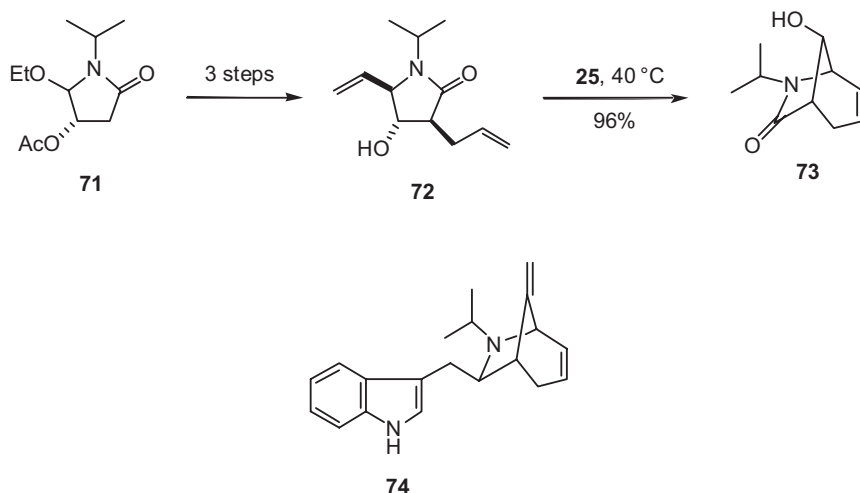


Scheme A.2-13

Approach to Synthesis of vellosimine (70) In the context of developing new approaches to the sarpagine family of indole alkaloids, of which vellosimine (**70**) is a representative member [31], we applied RCM to the synthesis of the bridged indole derivatives **68** and **69** [32]. Thus, the dihydrocarboline **64**, which was prepared in one pot from tryptophan according to prior art [33], was converted in two steps into **65** (Scheme A.2-14). The stereocenter at C(3) in **65** was set by the stereoselective (5.4:1) addition of trimethylallylsilane to an acyl iminium ion. The ester **65** was then transformed via different one-pot operations into diene **66** as well as enyne



Scheme A.2-14

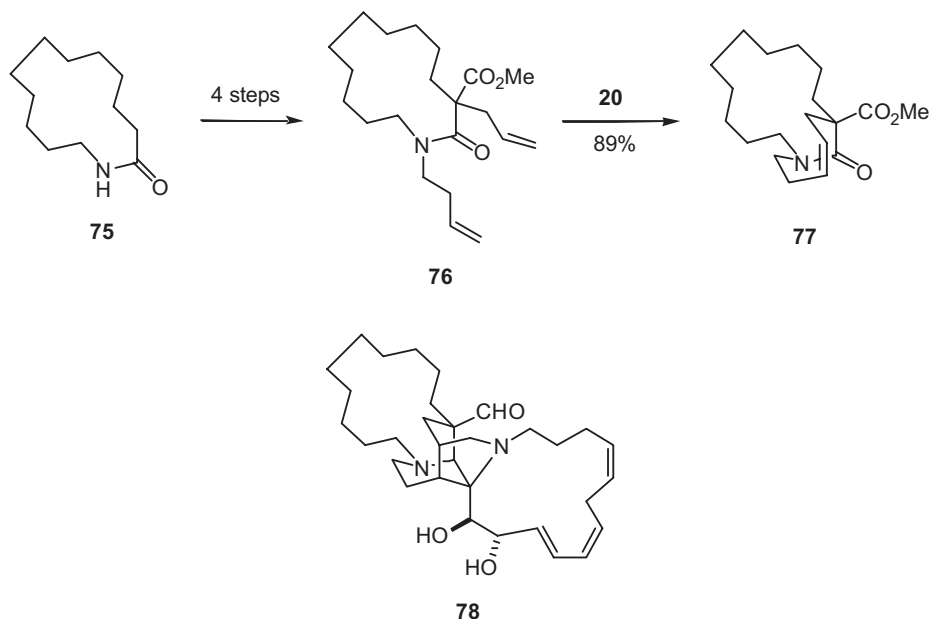


Scheme A.2-15

67. When **66** was treated with Grubbs catalyst **20** at room temperature, **68** was obtained in nearly quantitative yield. Furthermore, **67** underwent facile enyne metathesis in the presence of **20** to give **69**. The conversions of compounds related to **68** and **69** into sarpagine alkaloids such as **70** are the subject of current investigations.

Formal synthesis of (–)-peduncularine (74) (–)-Peduncularine (**74**) is a structurally interesting indole alkaloid that has been the focus of a number of synthetic efforts owing to its anticancer activity and the presence of an unusual 6-azabicyclo[3.2.1]-3-octene subunit in its structure [34]. Our own interest in **74** was piqued by the possibility that an RCM reaction might be used to form this bridged bicyclic skeleton, and we have recently implemented such a cyclization as the key step in a concise formal synthesis of peduncularine (Scheme A.2-15) [35]. The lactam **71**, which was prepared in two chemical operations from (*S*)-malic acid by simple modification of a known procedure for the synthesis of a similar compound [34a], was elaborated into **72** in good overall yield. Although **72** did not undergo RCM using **20** as the catalyst, heating **72** with the more reactive catalyst second generation **25** gave **73** in nearly quantitative yield. The bicyclic lactam **73** had been previously converted into (–)-peduncularine (**74**) by Speckamp [34a], and its preparation therefore constitutes a formal synthesis of this alkaloid.

Approach to sarain A (78) We recently initiated some exploratory studies directed toward the complex marine alkaloid sarain A (**78**) [36]. A key intermediate in the planned synthesis was the bridged bicyclic lactam **77**, which constitutes the AB ring system of the natural product (Scheme A.2-16) [37]. Thus, lactam **75**, which was prepared from cyclododecanone via a Schmidt reaction, was converted to **76** via a straightforward sequence of four reactions. The cyclization of **76** to give **77** by RCM using **20** as catalyst proceeded smoothly and in excellent yield. Efforts to



Scheme A.2-16

convert 77 into sarain A are ongoing, and the results of these investigations will be reported in due course.

Conclusions

Only a decade has elapsed since Grubbs discovered that the Schrock catalyst 3 could be used to induce efficient cyclizations of functionalized substrates via RCM. Since those early reports, there has been a virtual explosion of research in the area, as is evident from the compilation of results in numerous reviews on the subject and in the present treatise [38]. Improved catalysts are being continuously developed, and there are an increasing number of applications of RCM to problems in organic synthesis, chemical biology, and material science. Indeed, the synthesis of the tetracyclic manzamine model 18, which represents one of the first such applications, clearly established that highly functionalized substrates could undergo efficient RCM to produce complex structures. Consequent to this discovery, we have been involved in applying RCM to fundamental problems in alkaloid total synthesis. Indeed, we have found that RCM may be exploited as a key step in designing new entries to numerous families of alkaloids. Although an early focus was upon applying RCM to form the fused nitrogen heterocycles that constitute subunits of many indole alkaloids, we have more recently discovered that RCM may be employed to fabricate a variety of different bridged bicyclic systems as well. It is fair to predict that the future holds the promise of even more advances, not only in alkaloid chemistry but in other arenas as well.

Acknowledgments

I am especially grateful to have had the good fortune to work with an outstanding group of undergraduate and graduate students as well as postdoctoral associates over the years. The names of those who have contributed to the present work are found in their papers cited herein. I also wish to thank the National Institutes of Health, the Robert Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their ongoing support of our research.

References

- (a) GRUBBS, R. H.; FU, G. C. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427.
(b) GRUBBS, R. H.; FU, G. C. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.
- (a) SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DiMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886. (b) BAZAN, G. C.; KHOSRAVI, E.; SCHROCK, R. R.; FEAST, W. J.; GIBSON, V. C.; O'REGAN, M. B.; THOMAS, J. K.; DAVIS, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378–8387. (c) BAZAN, G. C.; OSKAM, J. H.; CHO, H.-N.; PARK, L. Y.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907.
- For example, RCM reactions had been used to prepare unsaturated macrocyclic lactones. See: (a) VILLEMIN, D. *Tetrahedron Lett.* **1980**, *21*, 1715–1718. (b) TSUJI, J.; HASHIGUCHI, S. *Tetrahedron Lett.* **1980**, *21*, 2955–2958.
- FORBES, M. D. E.; PATTON, J. T.; MYERS, T. L.; MAYNARD, H. D.; SMITH, D. W., JR.; SCHULTZ, G. R.; WAGENER, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978–10980.
- For reviews of the manzamine alkaloids, see: (a) MATZANKE, N.; GREGG, R. J.; WEINREB, S. M. *Org. Prep. Proc. Intl.* **1998**, *30*, 1–51. (b) MAGNIER, E.; LANGLOIS, Y. *Tetrahedron* **1998**, *54*, 6201–6258.
- (a) MARTIN, S. F.; LIAO, Y.; CHEN, H.-J.; PÄTZEL, M.; RAMSER, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005–6008. (b) MARTIN, S. F.; CHEN, H.-J.; COURTNEY, A. K.; LIAO, Y.; PÄTZEL, M.; RAMSER, M. N.; WAGMAN, A. S. *Tetrahedron* **1996**, *52*, 7251–7264.
- NEIPP, C. E.; MARTIN, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779–1782.
- (a) DESLONGCHAMPS, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, **1983**; Chapter 6. (b) STEVENS, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296.
- BROWN, J. D.; FOLEY, M. A.; COMINS, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445–7447.
- SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953–956.
- MARTIN, S. F.; LIAO, Y.; WONG, Y.; REIN, T. *Tetrahedron Lett.* **1994**, *35*, 691–694.
- (a) MARTIN, S. F.; HUMPHREY, J. H.; ALI, A.; HILLIER, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866–867. (b) HUMPHREY, J. H.; LIAO, Y.; ALI, A.; REIN, T.; WONG, Y.-L.; CHEN, H.-J.; COURTNEY, A. K.; MARTIN, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584–8592.
- SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- For a closely related RCM cyclization, see: PANDIT, U.; BORER, B.; BIERAUGEL, H. S. *Pure Appl. Chem.* **1996**, *68*, 659–662.
- FU, G. C.; NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
- For a synthesis of manzamine A via a different approach, see: WINKLER, J. D.; AXTEN, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425–6426.
- (a) FUKUYAMA, T.; XU, L.; GOTO, S. *J. Am. Chem. Soc.* **1992**, *114*, 383–384. (b) SCHKREYANTZ, J. M.; DANISHEFSKY, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722–4723. (c) KATO, T.; ITOH, E.; YOSHINO, T.; TERASHIMA, S. *Tetrahedron*

- 1997, 53, 10229–10238. (d) YOSHINO, T.; NAGATA, Y.; ITOH, E.; HASHIMOTO, M.; KATOH, T.; TERASHIMA, S. *Tetrahedron* **1997**, 53, 10239–10252. (e) KATOH, T.; NAGATA, Y.; YOSHINO, T.; NAKATANI, S.; TERASHIMA, S. *Tetrahedron* **1997**, 53, 10253–10270.
- 18 (a) MILLER, S. J.; KIM, S.-H.; CHEN, Z.-R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1995**, 117, 2108–2109. (b) RODRÍGUEZ, CASTEDO, L.; MASCAREÑAS, J. *Chem. Eur. J.* **2002**, 8, 2923–2930 and references therein.
- 19 MARTIN, S. F.; WAGMAN, A. S. *Tetrahedron Lett.* **1995**, 36, 1169–1170.
- 20 For a related study, see in reference 18a.
- 21 FELLOWS, I.; KAELEN, D. E.; MARTIN, S. F. *J. Am. Chem. Soc.* **2000**, 122, 10781–10787.
- 22 For a review of the Ergot alkaloids, see: NINOMIYA, I.; KIGUCHI, T. In *The Alkaloids*, BROSSI, A., Ed.; Academic Press: San Diego, CA, 1990; Vol. 38, 1–156.
- 23 For example, see: LIRAS, S.; LYNCH, C. L.; FRYER, A. M.; VU, B. T.; MARTIN, S. F. *J. Am. Chem. Soc.* **2001**, 123, 5918–5924.
- 24 LEE, K. L.; GOH, J. B.; MARTIN, S. F. *Tetrahedron Lett.* **2001**, 42, 1635–1638.
- 25 DIRAT, O.; VIDAL, T.; LANGLOIS, Y. *Tetrahedron Lett.* **1999**, 40, 4801–4802.
- 26 BUJARD, M.; BRIOT, A.; GOUVERNEUR, V.; MIOSKOWSKI, C. *Tetrahedron Lett.* **1999**, 40, 8785–8788.
- 27 DEITERS, A.; MARTIN, S. F. *Org. Lett.* **2002**, 4, 3243–3245.
- 28 For a review of Zr-catalyzed carbomagnesations see: BLUME, F.; SCHMALZ, H.-G. *Organic Synthesis Highlights IV*, **2000**, 77–82.
- 29 (a) AWANG, D. V. C.; VINCENT, A.; KINDACK, D. *Can. J. Chem.* **1984**, 62, 2667–2675. (b) STAHL, R.; BORSCHBERG, H.-J.; ACKLIN, P. *Helv. Chim. Acta* **1996**, 79, 1361–1378.
- 30 BAN, Y.; SETO, M.; OISHI, T. *Chem. Pharm. Bull.* **1975**, 23, 2605–2613.
- 31 For a leading reference, see: WANG, T.; COOK, J. M. *Org. Lett.* **2000**, 2, 2057–2059.
- 32 NEIPP, C. E.; MARTIN, S. F. *J. Org. Chem.* submitted.
- 33 MARTIN, S. F.; CHEN, K. X.; EARY, C. T. *Org. Lett.* **1999**, 1, 79–81.
- 34 For previous syntheses of peduncularine, see: (a) KLAVER, W. J.; HIEMSTRA, H.; SPECKAMP, W. N. *J. Am. Chem. Soc.* **1989**, 111, 2588–2595. (b) RIGBY, J. H.; MEYER, J. H. *Synlett* **1999**, 860–862. (c) ROBERSON, C. W.; WOERPEL, K. A. *Org. Lett.* **2000**, 2, 621–623. (d) LIN, X.; STIEN, D.; WEINREB, S. M. *Tetrahedron Lett.* **2000**, 41, 2333–2337.
- 35 WASHBURN, D. G.; HEIDEBRECHT, R. W.; MARTIN, S. F. *Org. Lett.* Submitted.
- 36 For some leading references to efforts directed toward the synthesis of sarain A, see: (a) DOWNHAM, R.; NG, F. W.; OVERMAN, L. E. *J. Org. Chem.* **1998**, 63, 8096–8097. (b) DENHART, D. J.; GRIFFITH, D. A.; HEATHCOCK, C. H. *J. Org. Chem.* **1998**, 63, 9616–9617. (c) IRIE, O.; SAMIZU, K.; HENRY, J. R.; WEINREB, S. M. *J. Org. Chem.* **1999**, 64, 587–595. (d) SUNG, M. J.; LEE, H. I.; CHONG, Y.; CHA, J. K. *Org. Lett.* **1999**, 1, 2017–2019.
- 37 STRAUB, C. S.; MARTIN, S. F. *Tetrahedron Lett.* Submitted.
- 38 For some reviews of RCM, see: (a) SCHUSTER, M.; BLECHERT, S. *Angew. Chem. Int. Ed.* **1997**, 36, 2037–2056. (b) SCHROCK, R. R. *Top. Organomet. Chem.* **1998**, 1, 1–36. (c) GRUBBS, R. H.; CHANG, S. *Tetrahedron* **1998**, 54, 4413–4450. (d) WRIGHT, D. L. *Current Org. Chem.* **1999**, 3, 211–240. (e) MAIER, M. E. *Angew. Chem. Int. Ed.* **2000**, 39, 2073–2077. (f) FÜRSTNER, A. *Angew. Chem. Int. Ed.* **2000**, 39, 3012–3043. (g) TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, 34, 18–29.

2.9 Vignette 3

Radicol and the Epothilones: Total Synthesis of Novel Anticancer Agents Using Ring-Closing Metathesis

Jon T. Njardarson, Robert M. Garbaccio, and
Samuel J. Danishefsky

In the evolution of synthetic methodology, new opportunities in natural product synthesis are often created. The ruthenium-based catalytic ring-closing metathesis reaction provided a striking and powerful alternative to existing coupling technologies in that it requires two unelaborated olefins as coupling partners, is tolerant to many functional groups, and can accommodate various ring sizes. This vignette describes recent efforts from our laboratory in which we applied the ring-closing metathesis reaction to strategic advantage and realized successful outcomes for two potentially important classes of anticancer agents: the radicol-like macro- lides and the epothilones.

Radicol (1) [1, 2] and monocillin I (2) [2] are resorcylic macro- lides that can both be isolated in limited quantities from *Monocillium nordinii* [2] (Figure A.3-1). Although both natural products and other members of this class exhibit a variety of antifungal and antibiotic properties, radicol (1) has recently come into focus for its anticancer potential. The ability of radicol (1) to suppress the transformed phenotype caused by various oncogenes such as *src*, *ras*, and *raf* has been linked to its inhibition of the Hsp90 molecular chaperone [3]. Interruption of Hsp90-assisted folding and downstream function of oncogenic proteins is of great clinical interest, as evidenced by the entry of geldanamycin (3) [4] into Phase I clinical trials for the treatment of cancer. Hence, the combination of growing interest in Hsp90 inhibition for the treatment of cancer and the high affinity of radicol (1) for this target prompted a study in my laboratory directed to its total synthesis [5]. In time, a concise synthesis was realized. Ring-closing metathesis proved to be a highly enabling resource in this effort.

At the outset, it was recognized that formation and maintenance of the epoxy-*cis*, *trans*-diene moiety (C8'-C3') within the 14-membered macro- lide constituted the core of the synthetic challenge (Figure A.3-2). As our strategy evolved, efforts came to rely on a three-component coupling of benzoic acid (4), vinyl epoxide (5), and an allylic acyl-anion equivalent (6) to construct the radicol-like macro- lide (Figure A.3-2). While palladium-catalyzed coupling protocols were considered to form the C4'-C5' junction, most required the generation of functionalized olefin partners

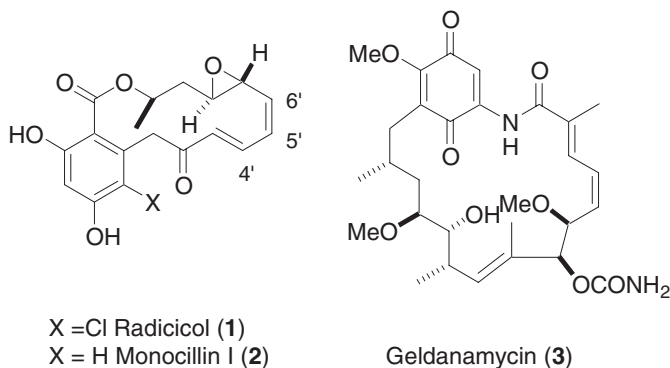


Fig. A.3-1. Structures of radicol, monocillin I, and geldanamycin.

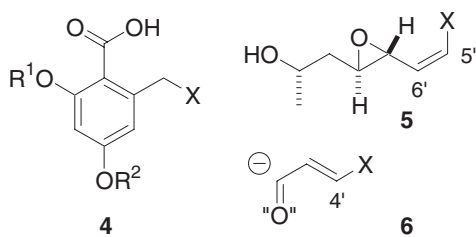
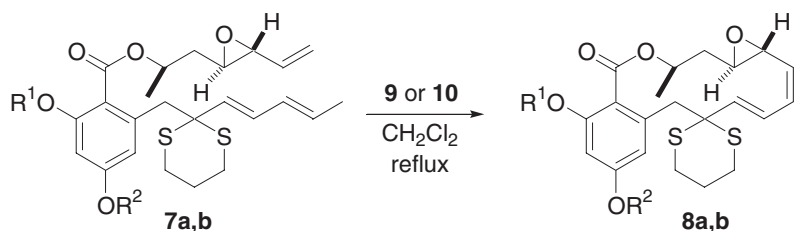


Fig. A.3-2. Synthetic strategy: three-component coupling.

(X = Sn, I, B, Zr) with specific geometry. It was envisioned that an unprecedented late-stage, stereospecific ring-closing metathesis reaction would obviate the requirement for elaborated, stereo-defined olefinic precursors and would serve to minimize transformations in an already sensitive environment. It was confidently expected that the constraints of the 14-membered ring would give rise to only the desired *cis*-geometry at C5'-C6' and that the potential formation of a 12-membered ring would not be competitive. Aside from this risk, the setting for the actual metathesis reaction posed some formidable issues: thus, the merger of a terminal vinyl epoxide (unprecedented as an RCM partner) with a conjugated internal diene had to take place in the presence of two sulfur atoms, notorious for their inactivation of ruthenium-based catalysts [6]. Thus, success of this venture was certainly not assumed as a matter of course.

In the event, despite numerous attempts, the ring-closing metathesis reaction of intermediate (**7a,b**) using the first-generation Grubbs catalyst (**9**) produced only trace amounts of the desired macrolide (**8a,b**) (Figure A.3-3). Fortunately, Grubbs and coworkers had issued reports on the synthesis and application of a highly active second-generation catalyst (**10**) [7] and, concurrent with our efforts, had reported its use in a cross-metathesis employing a vinyl-epoxide [8]. Following synthesis of the catalyst (commercially unavailable at the time), successful ring-closing



R ¹	R ²	catalyst	product	yield
Me	Me	9	8a	trace
Me	Me	10	8a	55%
TBS	TBDPS	9	8b	trace
TBS	TBDPS	10	8b	60%

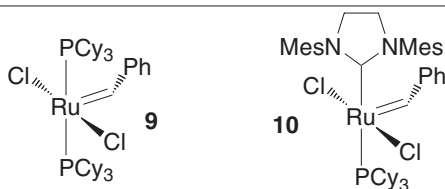


Fig. A.3-3. Ring-closing metathesis reaction.

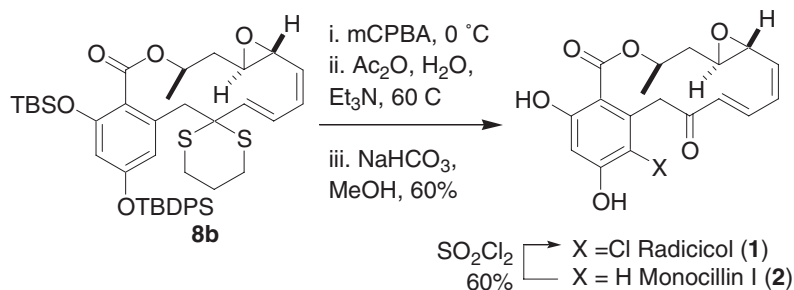


Fig. A.3-4. Completion of the synthesis.

metatheses were, in fact, achieved to fashion stereoselectively the 14-membered ring of radicicol in good yield. Commercial catalyst **10** produced similar, if not slightly superior, results.

For completion of the synthesis (Figure A.3-4), dispatch of the dithiane (**8b**) using the logic of the Pummerer reaction, followed by hydrolysis of the resulting phenolic acetates, resulted in global deprotection, giving rise to monocillin I (**2**). A regioselective chlorination was accomplished to convert (**2**) into radicicol (**1**). Clearly, advances in ruthenium-based olefin metathesis contributed enormously to this concise total synthesis of radicicol, a potential anticancer agent.

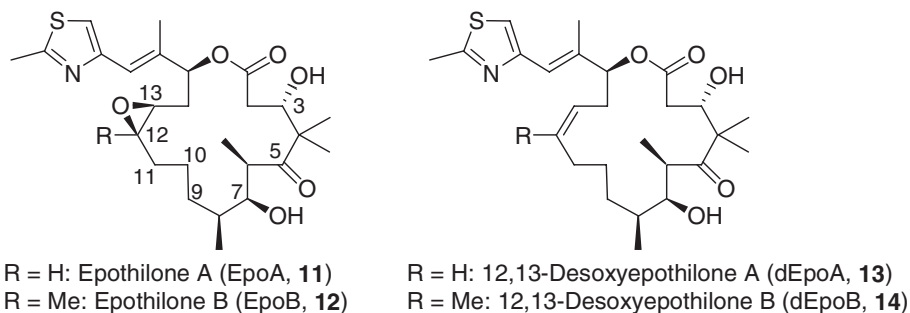


Fig. A.3-5. The epothilones.

In contrast to the recent investigation of Hsp90 inhibitors for the treatment of cancer, antimitotics have long been used in the clinic. The anticancer antimitotics are represented by vinblastine, taxol, and, more recently, the epothilones. Since their discovery, the epothilones have evoked much excitement among scientists. These cytotoxic macrolides originated from a mycobacterium of the genus *Sorangium* and were found to possess remarkable antitumor activities. The epothilones kill cells through a taxol-like (tubulin stabilization) mechanism of action. However, in contrast to taxol, they retained potency in MDR cell lines. This property raised the hope that epothilone-derived anticancer drugs might eventually be useful for the treatment of drug-resistant tumors. Our laboratory accomplished the first total synthesis of epothilone A (Figure A.3-5, **11**) and B (**12**). In addition we discovered that a minor component of the fermentation broth, 12,13-desoxyepothilone B (dEpoB, **14**), is more efficacious in xenograft mice models and dogs than are other naturally occurring epothilones containing 12,13-epoxides. Currently, multigram quantities of dEpoB have been obtained by total chemical synthesis. For the moment, material derived from biological means has been advanced to Phase I clinical trials. The ultimate preferred source of drug remains to be decided.

Ring-closing metathesis (RCM) has over the years played a continuing role in our discovery engine. It was the macrocyclization method proposed in an early approach that envisioned RCM to construct the 9–10 bond of the epothilones (Figure A.3-6) [9]. We were delighted when model system **15** provided macrocycle **16** in excellent yield using Grubbs' catalyst (**9**) [10]. We were correspondingly disappointed when we found that our seco-compound **17** and its variants failed to undergo the desired ring closure [11].

Our first total synthesis of epothilone A (**11**) was accomplished using an aldol-macrocyclization [12]. With our biology-based preference for the 12,13-desoxy agent and the need for a more practical synthesis to provide material for biological studies, we again turned our attention to olefin metathesis. We decided to explore the feasibility of constructing the 12–13 olefin using RCM to reach our desoxy compound (Figure A.3-7, **19**→**20**) [13]. This time around, the RCM occurred smoothly to construct silyl-protected dEpoA (**13**). The only problem was that the

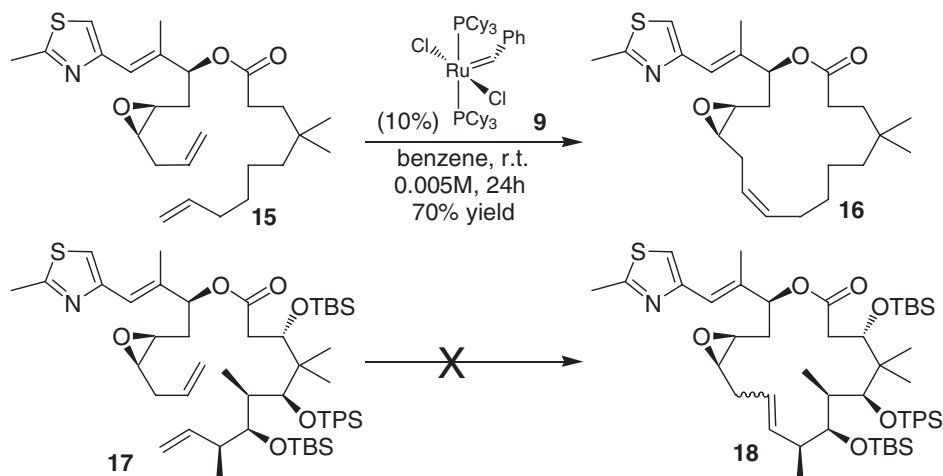


Fig. A.3-6. Ring-closing metathesis via the 9–10 bond.

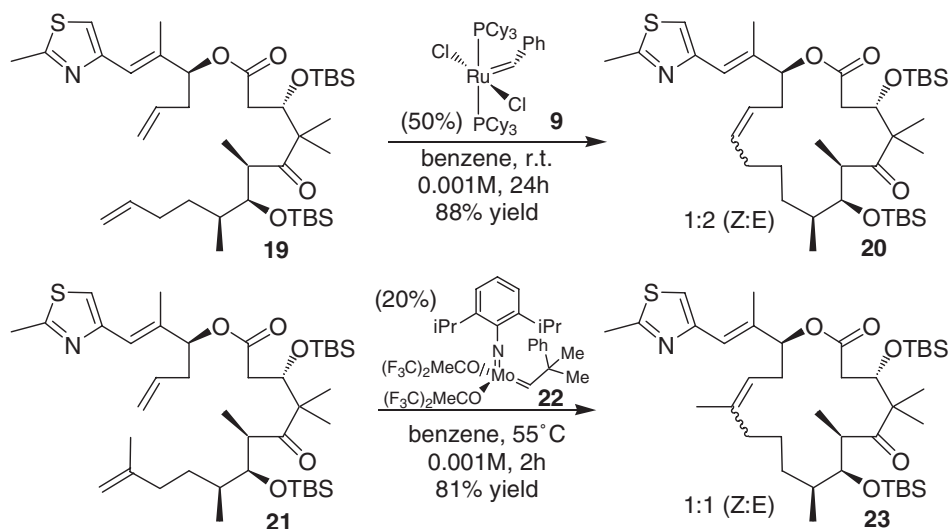
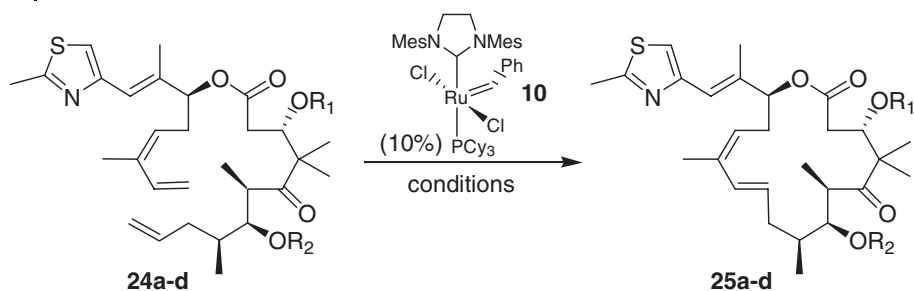


Fig. A.3-7. Ring-closing metathesis via the 12–13 bond.

olefin isomer ratio was virtually unity. Even more discouraging were the serious difficulties encountered in attempting to separate the two isomers. Unfortunately, despite focused research, we could not overcome these problems.

Using the same approach in constructing the 12–13 trisubstituted olefin required for dEpoB, we took recourse in the more reactive Schrock catalyst (**22**) to effect the macrocyclization [14]. Ring closure took place smoothly, but to our dis-



Substrate (24)	R ₁	R ₂	0.002 M in CH ₂ Cl ₂ ^a % yield (25)	0.002 M in toluene ^b % yield (25)
a	TES	Troc	35	58 ^c
b	H	Troc	41	57
c	TES	H	57	n.d. ^d
d	H	H	64	55

^a Reacted for 5.5 h at 35 °C

^b reacted for 25 min at 110 °C.

^c Done with 20 mol% catalyst at 0.0005 M dilution.

^d Not determined.

Fig. A.3-8. Ring-closing metathesis via the 11–10 bond.

may we were again confronted with the same problem of poor olefin isomer ratio and purification hardship (Figure A.3-7, **21**→**23**) [15].

The work detailed above was conducted prior to the introduction of Grubbs' second-generation catalyst (**10**). We have recently revisited the epothilone RCM problem in the context of our synthetic efforts towards a newly isolated epothilone derivative ddEpoB (**25d**) [16]. Our plan was to construct ddEpoB using a diene-ene RCM. This approach was reminiscent of the problem faced in our recent total synthesis of radicicol described above. In that case, we used the second-generation Grubbs' catalyst to effect a similar diene-ene RCM. In our latest approach we use diene-ene RCM to build the 10–11 bond. The results of our studies are summarized in Figure A.3-8 [7]. We were delighted to find out that the second-generation Grubbs catalyst effected the desired macrocyclization, producing only the desired E-isomer and thereby solving both of our previous problems. The yield of the RCM varied significantly with different substitution patterns of hydroxyls 3 and 7 when performed in refluxing dichloromethane. By changing the solvent to toluene at reflux, these differences were erased and the yield was uniformly high, again furnishing only the desired E-isomer. Following these studies, we have shown that one can selectively reduce the 10–11 olefin in very high yield using diimide, thus accomplishing the first total synthesis of ddEpoB as well as a new and improved route to dEpoB.

In summary, both the radicicol and epothilone programs have been influenced greatly by the olefin metathesis reaction as detailed above. We have applied RCM to construct not only radicicol but also the epothilone macrocycle in three different

phases. In so doing, we have learned much about the scope and limitations of RCM within the epothilone framework. The examples detailed above show how improvements in basic reaction methodology have clear, direct impact on natural product synthesis and thereby could serve to promote the advancement of cancer chemotherapy.

References

- 1 DELMOTTE, P.; DELMOTTE-PLAQUEE, J. *Nature* **1953**, 171, 344.
- 2 AYER, W. A.; LEE, S. P.; TSUNEDA, A.; HIRATSUKA, Y. *Can. J. Microbiol.* **1980**, 26, 766.
- 3 ROE, S. M.; PRODROMOU, C.; O'BRIEN, R.; LADBURY, J. E.; PIPER, P. W.; PEARL, L. H. *J. Med. Chem.* **1999**, 42, 260.
- 4 a) KUDUK, S. D.; ZHENG, F. F.; SEPP-LORENZINO, L.; ROSEN, N.; DANISHEFSKY, S. J. *Biorg. Med. Chem. Lett.* **1999**, 9, 1233. b) KUDUK, S. D.; HARRIS, C. R.; ZHENG, F. F.; SEPP-LORENZINO, L.; OUFERELLI, Q.; ROSEN, N.; DANISHEFSKY, S. J. *Bioorg. Med. Chem. Lett.* **2000**, 10, 4325.
- 5 (a) GARBACCIO, R. M.; DANISHEFSKY, S. J. *Org. Lett.* **2000**, 2, 3127. (b) GARBACCIO, R. M.; STACHEL, S. J.; BAESCHLIN, D. K.; DANISHEFSKY, S. J. *J. Am. Chem. Soc.* **2001**, 123, 10903.
- 6 ARMSTRONG, S. K.; CHRISTIE, B. A. *Tetrahedron Lett.* **1996**, 37, 9373.
- 7 (a) SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 953. (b) CHATTERJEE, A. K.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 1751.
- 8 CHATTERJEE, A. K.; MORGAN, J. P.; SCHOLL, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, 122, 3783.
- 9 (a) MENG, D.; SORESENSEN, E. J.; BERTINATO, P.; DANISHEFSKY, S. J. *J. Org. Chem.* **1996**, 61, 7998. (b) BERTINATO, P.; SORESENSEN, E. J.; MENG, D.; DANISHEFSKY, S. J. *J. Org. Chem.* **1996**, 61, 8000.
- 10 (a) SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem Int. Ed. Engl.* **1995**, 34, 2039. (b) GRUBBS, R. H.; MILLER, S. J.; FU, G. C. *Acc. Chem. Res.* **1995**, 28, 446.
- 11 This problem has recently been addressed and solved by Sinha and coworkers utilizing the second generation Grubbs catalyst. Sun, J.; Sinha, S. C. *Angew. Chem Int. Ed. Engl.* **2001**, 41, 1381.
- 12 BALOG, A.; MENG, D.; KAMENECKA, T.; BERTINATO, P.; SU, D-S.; SORESENSEN, E. J.; DANISHEFSKY, S. J. *Angew. Chem Int. Ed. Engl.* **1996**, 35, 2801.
- 13 (a) MENG, D.; SU, D-S.; BALOG, A.; BERTINATO, P.; SORESENSEN, E. J.; DANISHEFSKY, S. J.; ZHENG, Y-H.; CHOU, T-C.; HE, L.; HORWITZ, S. B. *J. Am. Chem. Soc.* **1997**, 119, 2733. (b) MENG, D.; BERTINATO, P.; BALOG, A.; SU, D-S.; KAMENECKA, T.; SORESENSEN, E. J.; DANISHEFSKY, S. J. *J. Am. Chem. Soc.* **1997**, 119, 10073.
- 14 SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DIMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, 112, 3875.
- 15 These same problems were also encountered by other researchers. (a) YANG, Z.; HE, Y.; VOURLLOUMIS, D.; VALLBERG, H.; NICOLAOU, K. C. *Angew. Chem Int. Ed. Engl.* **1997**, 36, 166. (b) NICOLAOU, K. C.; HE, Y.; VOURLLOUMIS, D.; VALLBERG, H.; ROSCHANGAR, F.; SARABIA, F.; NINKOVIC, S.; YANG, Z.; TRUJILLO, J. I. *J. Am. Chem. Soc.* **1997**, 119, 7960. (c) NICOLAOU, K. C.; VALLBERG, H.; KING, N. P.; ROSCHANGAR, F.; HE, Y.; VOURLLOUMIS, V.; NICOLAOU, C. G. *Chem. Eur. J.* **1997**, 3, 1957. (d) NICOLAOU, K. C.; KING, N. P.; FINLAY, M. R. V.; HE, Y.; ROSCHANGAR, F.; VOURLLOUMIS, D.; VALLBERG, H.; SARABIA, F.; NINKOVIC, S.; HEPWORTH, D. *Bioorg. Med. Chem. Lett.* **1999**, 7, 665. (e) MAY, S. A.; GRIECO, P. A. *Chem. Commun.* **1998**, 1597. (f) SINHA,

- S. C.; BARBAS, C. F., III.; LERNER, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, 95, 9642. (g) SINHA, S. C.; SUN, J.; MILLER, G.; BARBAS, C. F., III.; LERNER, R. A. *Org. Lett.* **1999**, 1, 1623.
- 16** ARSLANIAN, R. L.; TANG, L.; BLOUGH, S.; MA, W.; QIU, R-G.; KATZ, L.; CARNEY, J. R. *J. Nat. Prod.* **2002**, 65, 1061.
- 17** BISWAS, K.; LIN, H.; NJARDARSON, J. T.; CHAPPELL, M. D.; CHOU, T-C.; GUAN, Y.; TONG, W. P.; HE, L.; HORWITZ, S. B.; DANISHEFSKY, S. J. *J. Am. Chem. Soc.* **2002**, 124, 9825.

2.10

The Use of Olefin Metathesis in Combinatorial Chemistry: Supported and Chromatography-Free Syntheses

Andrew M. Harned, Donald A. Probst, and Paul R. Hanson

2.10.1

Introduction

The recent growth of high-throughput screening for biologically active agents has increased the demand for new technologies to expedite the generation of diverse libraries of synthetic compounds. The concurrent advent of well-defined, homogeneous catalysts (Figure 2.10-1) has prompted the use of olefin metathesis toward both supported syntheses and other chromatography-free synthetic methodologies that can be implemented in combinatorial chemistry. Olefin metathesis has proven to be a remarkably general technique and has acquired widespread use in combinatorial chemistry despite the general difficulty in transferring solution-phase chemistry to a solid support. In an effort to encapsulate the growing potential of this enabling technology, a chapter devoted to the use of metathesis in combinatorial chemistry is both timely and practical.

One can conceive of many ways to dissect the rapidly growing body of work in this field: the type of support, the libraries constructed, or the type of metathesis reaction performed. We have chosen the latter. Supported syntheses rely heavily on ring-closing metathesis (RCM) and cross-metathesis (X-MET), while chromatography-free reagents and new support designs rely heavily upon ring-opening metathesis polymerization (ROMP). In addition, hybrid examples such as ring-opening metathesis/cross-metathesis (ROM/X-MET) will also be discussed.

Unfortunately, supported synthesis is not so easy to categorize. It is commonly viewed as consisting of three parts: the support, a linker, and the compound being synthesized. The support can be anything from a solid bead (i.e., cross-linked polystyrene) to a soluble polyether (such as polyethylene glycol), to high-load soluble ROM oligomers. The compound being synthesized is self-explanatory, and the linker is the most difficult to define. One could surreptitiously define it as anything that is not support or compound. This definition is unsatisfactory in many cases, as linkers can be as small as a single atom (arguably part of the support) or be at least partially incorporated into the compound during cleavage, such as the case with cyclorelease (*vide infra*) using RCM. Current metathesis techniques on supported-phase synthesis and solution-phase library synthesis make good use of the versatility of the various types of olefin metathesis.

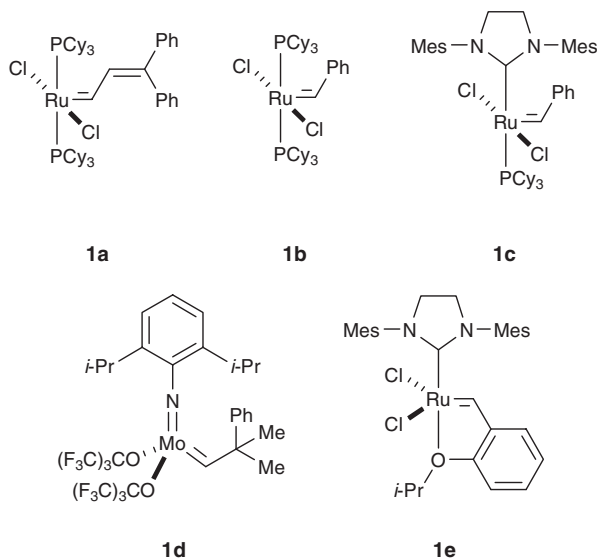


Fig. 2.10-1. Examples of the most widely used olefin metathesis catalysts.

2.10.2

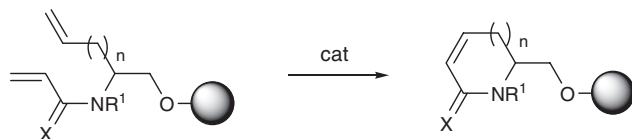
Metathesis Reactions Toward Supported Synthesis and Library Generation

2.10.2.1

Ring-Closing Metathesis (RCM)

RCM on solid supports

Numerous RCM approaches to library synthesis have been developed, and many have centered on the synthesis of cyclic polypeptides. In 1996, Blechert carried out the first of two general studies done to validate RCM on solid supports. First, trityl resin-bound allylamines were allylated and subjected to catalyst **1a**, yielding heterocyclic products in excellent yields (Scheme 2.10-1) [1]. The RCM of these diallylamines was also shown to be quite tolerant of α - α' substitution. Note, however, that a typical reaction time was 5 days in benzene at 30 °C. As expected, reaction times dropped significantly when catalyst **1b** was used in refluxing CH₂Cl₂.



2 $n = 0$; R¹ = Tosyl; X = H,H; cat = **1a**

4 $n = 1$; R¹ = Tosyl; X = H,H; cat = **1a**

6 $n = 1$; R¹ = H; X = O; cat = **1a**

8 $n = 1$; R¹ = COCF₃; X = H,Ph; cat = **1b**

3 $n = 0$; R¹ = Tosyl; X = H,H

5 $n = 1$; R¹ = Tosyl; X = H,H

7 $n = 1$; R¹ = H; X = O

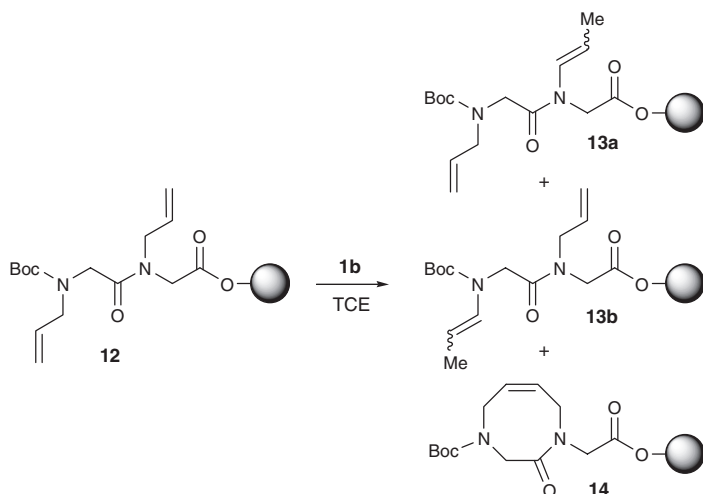
9 $n = 1$; R¹ = COCF₃; X = H,Ph

Scheme 2.10-1



The syntheses of cyclic peptides of various sizes lend themselves to RCM on a solid phase. Since the peptides can be synthesized using typical solid-phase methods, allyl and vinyl glycines (among other allylated species) can be readily introduced. Allylglycine was used in the synthesis of hexapeptide **10**, which was subjected to catalyst **1b** for 22 hours (Scheme 2.10-2) in analogy to the solution-phase reaction. The authors report that after cleavage, two substances were observed in a 3:2 ratio, the minor peak being the acyclic peptide and the major being the *trans* RCM product **11** [4].

Later studies found that some other peptides proved considerably more difficult to cyclize via RCM [7]. The poor reactivity appears unrelated to ring size, stereochemical orientations, or positions/lengths of the olefin-containing appendages,



Scheme 2.10-3

indicating that the secondary structure of the peptides themselves was prompting the failure of the RCM. This is consistent with an earlier finding that higher temperatures were required to afford RCM on dipeptides [5]. Realization that proline was present in all previous cases of RCM on larger peptides (>5 residues) further corroborates this hypothesis. The inclusion of Ser($\Psi^{\text{Me,Me}}$ pro) enables RCM to take place in good to excellent yields on trityl polystyrene resin, thereby allowing a small library of linear peptidyl resins to be synthesized and metathesized to >90% yield (Figure 2.10-2). It is interesting to note that on model compounds, purification was problematic of the cleaved peptides, which remained highly colored even after RP-HPLC and precipitation. The peptide could be purified by incubation with dithiothreitol (which forms a water-soluble Ru complex) and subsequent precipitation of the peptide in water.

The RCM reaction in peptides has served not only to stabilize secondary structures but also as a biosteric replacement of disulfide bridges [8]. Oxytoxin is a 9-membered peptide with a disulfide linkage between two cystine residues. Replacement of the cystines with allylglycines yielded the dicarba analogue as a 4:1 mixture of *cis* and *trans* isomers. Since the final product contains the reduced bond, selectivity is not critical.

Another technique used to generate arrays of cyclic peptides is deemed “rolling loop scan” [9]. This technique involves the synthesis of multiple peptides by systematically “moving” an olefinic chain down the peptide in fixed increments, i.e., attachment of an olefin to each successive backbone nitrogen within the library, then subjecting the mixtures of peptide beads to RCM conditions, producing a library of cyclic peptides with varying connectivities.

Verdine and coworkers demonstrated the combinatorial potential of supported RCM through the synthesis of a library of 320 nitroso-linked dienes on a polystyrene-based trityl resin for use as cell-permeable molecules. Upon subjection

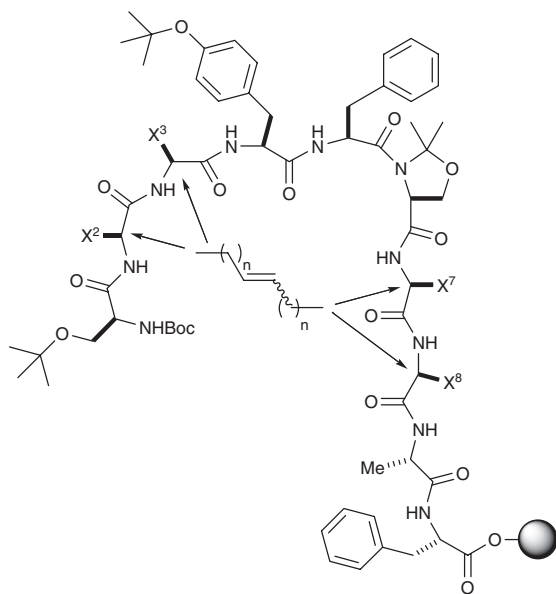


Fig. 2.10-2. RCM on racemic olefinic peptides, including Asn²/Asn⁷, Asn²/Ile⁸, Lys³/Asn⁷, and Lys³/Ile⁸ with different lengths of bridging side chain $n = 2$ and $n = 3$. X²–X⁸ are either bridging side chains or naturally occurring protected amino acid side chains.

to RCM conditions using catalyst **1b** in CH₂Cl₂ for 1 hour, each nitroso-linked diene in the library underwent RCM to give complete conversion to a single cyclic product (Figure 2.10-3) [10].

One shortfall to RCM is the loading density of the supports. In the course of examining RCM reactions on solid supports, it was noted that some X-MET was unavoidable [11]. In fact, when a monoolefin was resin-bound it underwent facile X-MET, yielding 70–84% of the dimer (using 30 mol% **1b**), with 8–20% starting material recovered after cleavage. Some syntheses have actually taken advantage of this phenomenon and will be discussed in the X-MET portion of this chapter.

One can generate considerable complexity by combining different metathesis elements into an integrated approach as shown by Schreiber et al. in their diversity-oriented synthesis of “natural product-like” molecules [12]. This strategy consists of ring-opening/ring-closing metathesis yielding the fused tetracycle **16** in a single step as shown in Scheme 2.10-4.

Supported RCM is not limited to the solid phase. An example exists of making cyclic amino acids **21** on a soluble, PEG-supported sulfonyl linker **17** (Scheme 2.10-5) [13]. The RCM was achieved using either **1b** or **1c** in excellent yields generating cyclic amino acids from 6- to 8-membered rings. In addition, soluble ROM supports have been utilized for carrying out RCM reactions (see “RCM on Soluble ROM Supports” section).

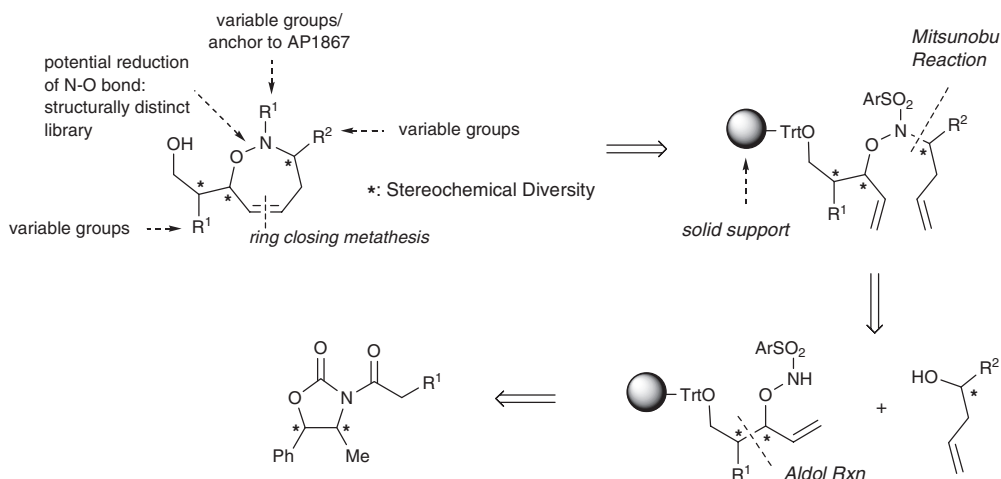
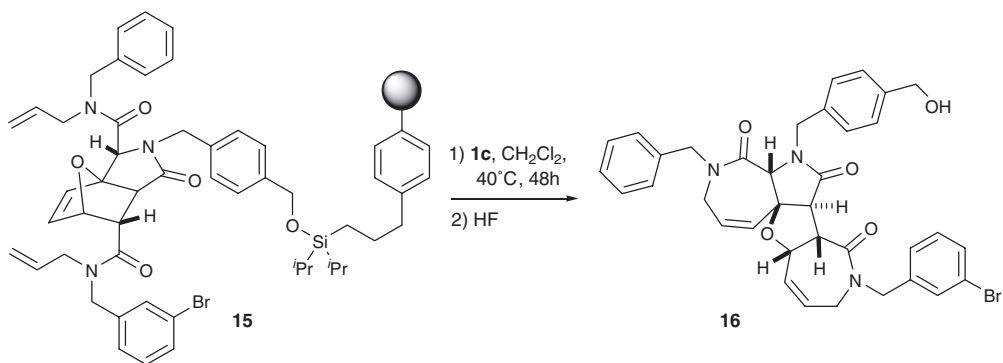


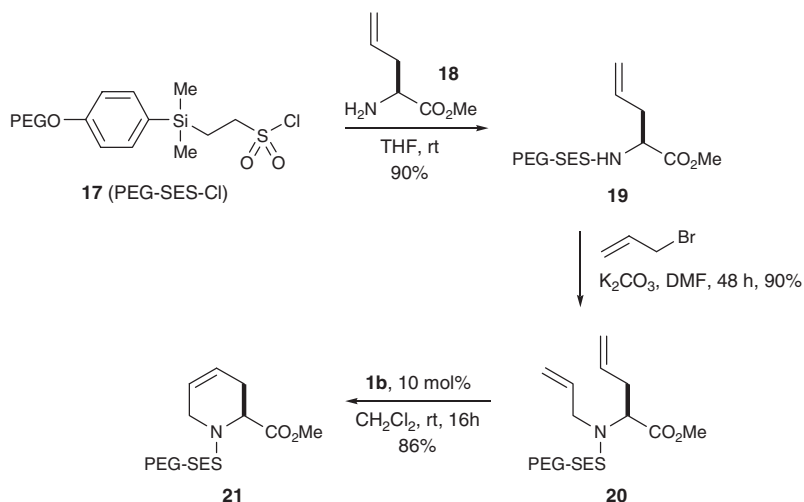
Fig. 2.10-3. Retrosynthetic analysis of a library of cell-permeable molecules using RCM on a solid support.



Scheme 2.10-4

RCM linkers: cyclorelease strategies

RCM can also be used as a cleavage step in a process known as cyclorelease. As shown in Figure 2.10-4, there are two basic strategies for cyclorelease using RCM, both involving an olefin within the linker. If the other olefin involved in the metathesis reaction is part of the product molecule, the cleavage will yield a cyclic product and terminal support (Type I). If, on the other hand, both olefins are part of the linker, the RCM will yield a terminal olefin as part of the product (Type II). This flexibility has been widely explored; however, some general problems arise, including generally poor yields (~50%), optimization of linkers for each library, and the reliance on cofactors (a small molecule olefin source). Many of these problems are the result of the functional density of the solid support itself, allowing facile X-MET or other cross-reactions.



Scheme 2.10-5

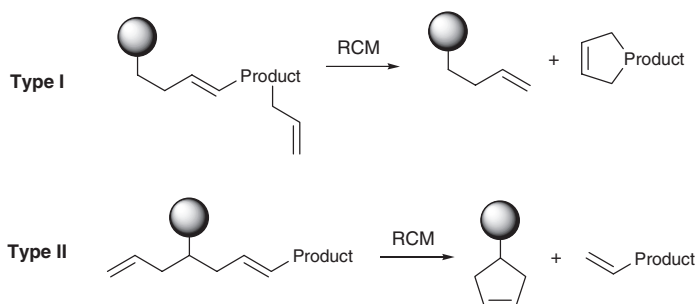


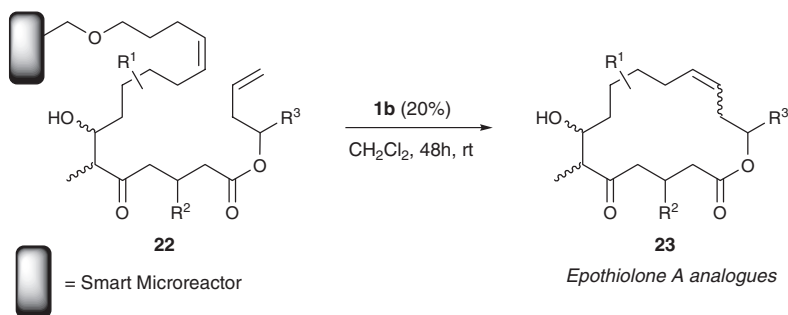
Fig. 2.10-4. General cyclorelease strategies, producing either a cyclic or terminal olefin on the product.

Cyclorelease yielding cyclic products Further examination of Figure 2.10-4 shows the inherent problem with cyclorelease. Assuming the metathesis event initiates at the terminal olefin, the catalyst will be bound to the resin after ring closure. It is therefore necessary either to use 100 mol% of catalyst or to add a co-reagent to free the catalyst. The first example of RCM cyclorelease explored the synthesis of lactams on a Merrifield resin using an olefinic linker [14]. Table 2.10-1 (entries 1–5) shows conditions required and cleavage obtained. Unexpectedly, the stoichiometric use of **1b** yielded only 54% of the product, suggesting that cross-metathesis was occurring on the bead. Later studies showed that several minor changes are key to the successful cyclorelease, including changes in linker, substitution of a benzoate derivative for a phenolic derivative, and the use of styrene as a co-additive (Table 2.10-1, entries 6 and 7) [15].

Cyclorelease strategies have also proven successful toward tetrapeptides, with yields dependent on linker lengths [16]. Shorter, substituted styrenyl linkers have

Tab. 2.10-1. Conditions for cyclorelease of 7-membered lactam.

Entry	% Catalyst 1b	Cofactor	Temp (°C)	Reaction time	Yield
1	14	Ethylene	23	7 days	5%
2	30	Ethylene	23	2 days	44%
3	12	1-octene	23	7 days	32%
4	12	1-octene	50	2 h	37%
5	100	–	50	16 h	54%
6	5	Styrene	50	18 h	86%
7	5	Styrene	80	18 h	80%



Scheme 2.10-6

been utilized with success as well in the synthesis of aldol-derived peptidomimetics [17], pipercolinates [18], dihydropyrans [18], and lactams [18–20]. Cyclorelease has been utilized in the rapid solid-phase synthesis of Freidinger lactam β -turn mimics in excellent yield (61% overall) and purity (>95%) without chromatographic purification [20] as well as sultam derivatives of Freidinger lactams [21]. The sultam synthesis not only exploited an RCM cyclorelease but also explored the use of “dual-armed” linkers, effectively doubling the load capacity of resins with little or no loss in overall yield.

The technique is not limited to small molecules, as epothilones A and B have been synthesized by Nicolaou and coworkers on a solid support and liberated via cyclorelease RCM [22]. They also utilized cyclorelease in the generation of libraries of designed epothilone analogues (Scheme 2.10-6) [23].

Cyclorelease yielding terminal olefin products An underutilized cyclorelease method involves the RCM toward cyclic linker residues on the supports, expelling the product containing a terminal olefin (Type II cyclorelease). A small library of styrene derivatives has been synthesized through this route [24]. Oligosaccharides, both linear [25] and branched [26], have been synthesized via solid-phase RCM cyclorelease in comparatively good to excellent yields (50–86%) as well. It should also be noted that the majority of “cyclorelease” linkers can be released via cross-metathesis as well; however, these examples will be discussed at the end of the following section.

2.10.2.2

Cross-Metathesis (X-MET)

One of the limitations of X-MET in solution is the control of product, i.e., does one achieve dimerization or true X-MET or some combination thereof. Despite aforementioned problems involving X-MET on solid supports [11], it remains a viable option for limiting X-MET dimerization.

Ene-ene cross-metathesis on solid supports

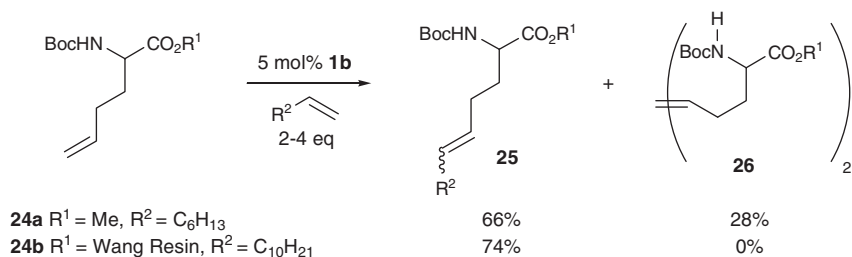
Resin-bound allylic and branched homoallylic amines were subjected to catalyst **1b** and various alkenes (3 equivalents) to afford X-MET products in fair to excellent yields (46–95%), depending on the nature of the olefin used, with more lipophilic olefins generating higher yields. *E:Z* ratios also varied widely with the olefin used without evident rationale.

X-MET of homoallyl glycine **24a** with various aryl- and alkyl-substituted olefins in solution invariably yielded some homodimers **26** of the amino acid (Scheme 2.10-7) [27]. This side reaction could be eliminated by attachment of the homoallyl glycine to a resin (**24b**) prior to X-MET. Note that a twofold excess of one of the olefins is still necessary in solution and a fourfold excess is required on solid-phase.

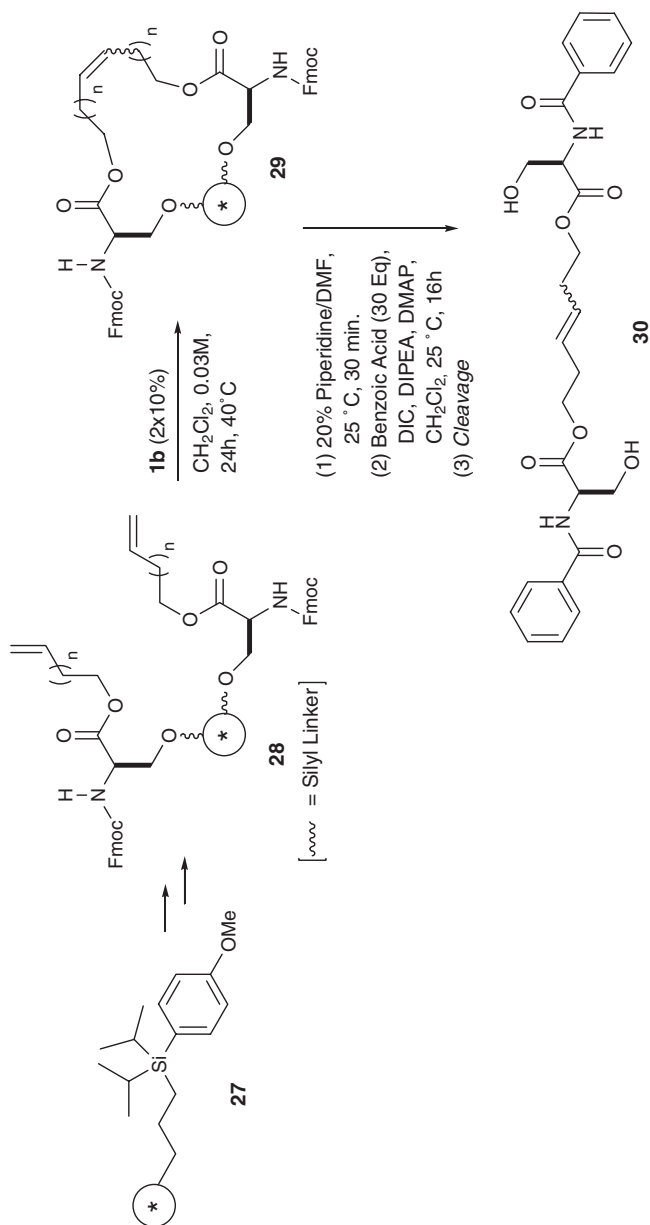
An efficient synthesis of hydroxyl *E*-stilbenoids was also undertaken on solid supports [28]. 4-Vinylphenol was immobilized on a Merrifield resin and exposed to 20 mol% catalyst **1b** along with a substituted styrene (10 equivalents) in benzene at 80 °C for 12 hours. These conditions yielded 61–81% overall (including loading and cleavage) of exclusively *E*-stilbenes in high (>95%) purity. The electronic variations on the styrenes appear to play little or no role in metathesis yield.

Cyclic oligoesters have been synthesized using X-MET as well [29]. A terminal olefin is attached through an ester linkage to a cross-linked polystyrene bead. X-MET is then used to affix olefins containing a hydroxyl group. The products are released through a novel cyclorelease/macrolactonization.

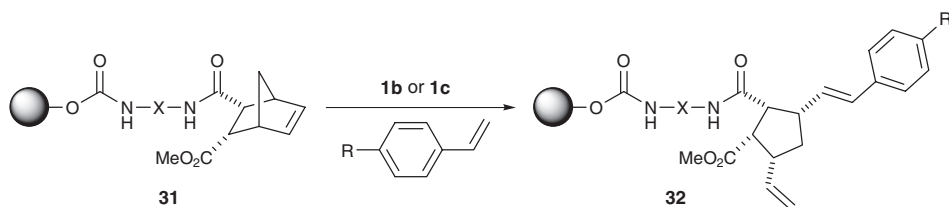
Another strategy is to take advantage of the close packing of functionalities on the resin to afford desired homodimers (Scheme 2.10-8) [30]. Using a silyl linker, Schreiber and coworkers attached amino esters, containing olefinic ester moieties, to a polystyrene bead. X-MET using 5 mol% of either **1b** or **1c** afforded X-MET dimers in generally >90% yields. At higher catalyst loadings, the styrene X-MET



Scheme 2.10-7



Scheme 2.10-8



Scheme 2.10-9

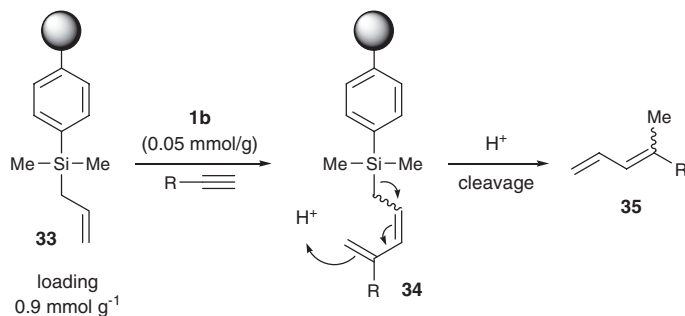
product is also observable, arising from either the first catalytic cycle or from styrene liberated in the first cycle. Peptides have been linked to Rink resin as well and cross-metathesized twice at 25 °C with 15 mol% catalyst **1b** [31].

Ring-opening cross-metathesis (ROM/X-MET), a subset of X-MET, has also been performed on solid supports [32, 33]. This technique is fundamentally similar to ROMP, whereby a strained cyclic olefin is opened by the catalyst and the substrate-bound catalyst undergoes X-MET with another olefin to yield the ring-opened product. When R is a strong electron-donating group (OH, OR), a relatively high regioselectivity is observed (~3:1) [32]. When R is an electron-withdrawing group or a weak donor, selectivities are lower, on the order of 1–1.5:1. The favored regioisomer is shown in Scheme 2.10-9.

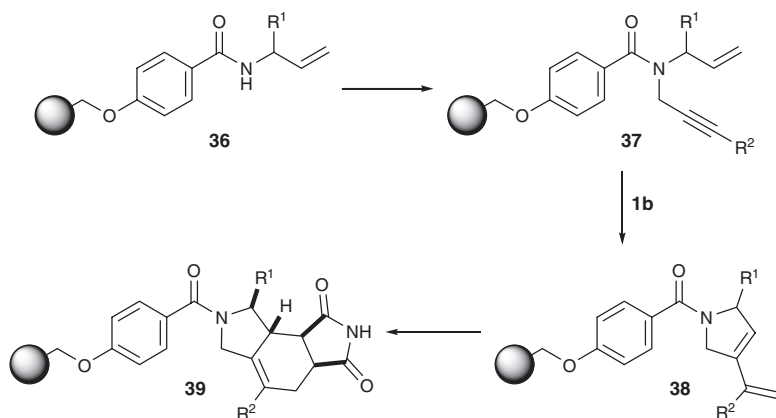
Enyne cross-metathesis and RCM

Enyne metathesis is quite useful in that it yields conjugated dienes, which are readily converted to other functional groups [34]. Both the olefin and the alkyne have been immobilized on the resin. Allylsilyl polystyrene resin **33** has been used as the olefinic partner [35], and a variety of alkynes have been coupled to it (Scheme 2.10-10). This support was chosen in part for its mild acidic cleavage conditions, which liberated the product diene **35**.

Alternatively, the alkyne can be immobilized on a resin. Using a dicarboxylic acid linker, propargylic alcohol was immobilized on Merrifield resin [36, 37]. The olefin is then added, with 10 mol% **1b**. The resulting diene is then subjected to a MeAlCl₂-catalyzed Diels-Alder reaction, yielding highly functionalized cyclohexane



Scheme 2.10-10



Scheme 2.10-11

derivatives. A similar sequential reaction can be performed with the olefinic component immobilized as well [36].

Enyne RCM coupled with the Diels-Alder reaction can rapidly lead to highly complex ring systems [38]. Immobilized allyl amine **36** was propargylated, subjected to enyne RCM, and followed by Diels-Alder addition to form tricycle **39** (Scheme 2.10-11).

X-MET and linkers

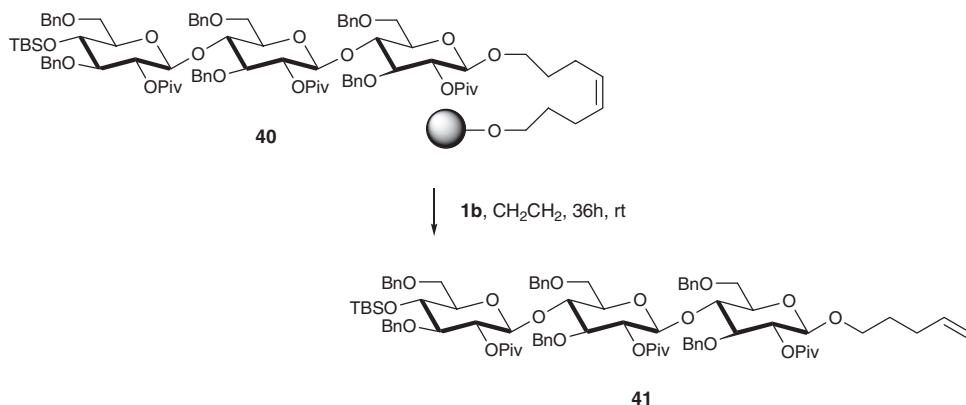
Oligosaccharides have been synthesized on an olefinic support and sequentially elaborated and cleaved via X-MET through the use of an octenediol linker [39]. The idea was further elaborated into a “protected” olefinic linker, in which the olefin was brominated, the oligosaccharides were synthesized, and the olefin was unmasked by tetrabutylammonium iodide and 4-butanone [40]. The unmasked olefin was then cleaved via X-MET (Scheme 2.10-12).

Cleavage is not the sole function X-MET has played in linker chemistry. The allyl silane linker shown in Scheme 2.10-10 has also been used in other supported syntheses. X-MET is used to load the desired substrate onto the resin [41], and electrophilic cleavage yields products in which the olefin-bound chain was extended by one carbon. In the case of allylic esters, cleavage produced the free acid.

X-MET in other library synthesis applications

Metathesis can also be used in other techniques toward library synthesis. While numerous libraries have been synthesized in which RCM was performed, but did not directly diversify the library, we have chosen to focus on the power of metathesis as either a diversification tool or a tool to “stitch” together a prearranged target.

One idea in this technique is to allow molecules to arrange themselves on a



Scheme 2.10-12

template or as aggregates and then use metathesis to lock them into that conformation; this is sometimes known as “dynamic combinatorial chemistry.” RCM has been used to lock π -associated catenanes into interlocking catenane links [42]. A ring-closing cross-metathesis technique has also been used to immobilize hydrogen-bonded assemblies of calixarenes using a temporary H-bonding “linker” to create macrocycles of calixarenes [43]. The temporary H-bonding linkers are then simply washed away.

Alternatively, one can use X-MET to couple fragments known (or at least likely) to bind to a given receptor in a directed or receptor (target)-assisted synthesis. This technique has been used to generate libraries of receptor-binding diols, which are then assayed competitively with each other to find the highest binding affinity ligands, which then direct the second-generation library [44]. Nicolaou and co-workers carried out a powerful example of this strategy [45]. In this work, vancomycin dimers were connected through an assortment of linkers at various points to develop activity against vancomycin-resistant bacteria (Figure 2.10-5).

The use of X-MET toward library diversification is by no means limited to template-driven approaches. Even the very simplest X-MET can produce astonishing diversity, as shown in Figure 2.10-6. This rapid method of diversification has been taken advantage of in numerous syntheses. By adding a second olefin, this type of strategy has rapidly produced vast libraries of X-MET products, which were utilized in the synthesis of oleic acid derivatives [46] and glycolipids [47]. Verdine and coworkers [48, 49] have utilized RCM on temporary silicon tethers [50] to generate libraries of X-MET-like *cis*-1,5-diols with exclusive *Z*-olefin stereochemistry [51].

The work of Boger et al. is perhaps the best-known showcase for X-MET generated libraries [52–54]. The general approach (Scheme 2.10-13) begins with a library of differentiated bis-amides **42**, which are subjected to X-MET with each other to form **43**.

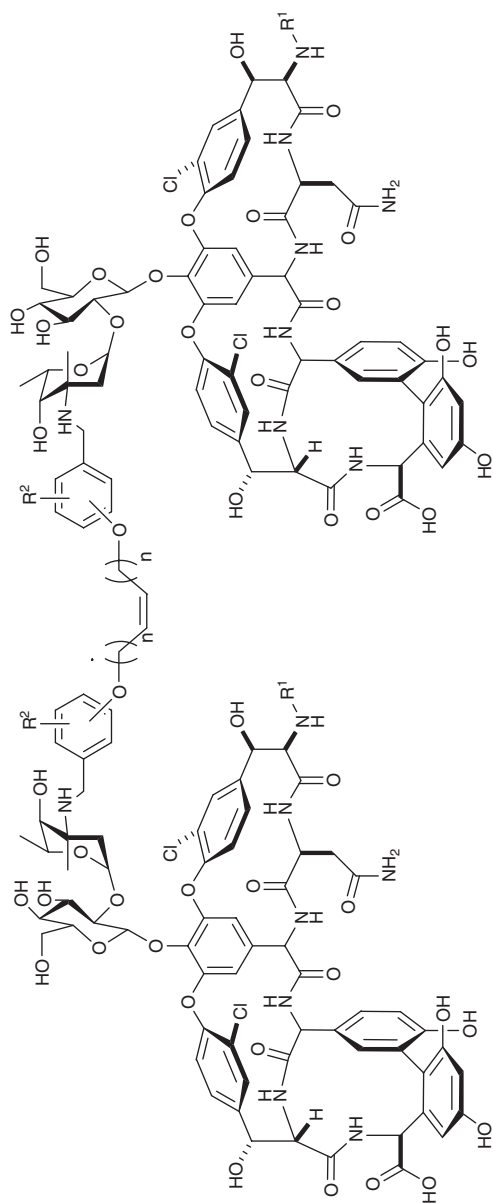


Fig. 2.10-5. Vancomycin dimers of Nicolaou.

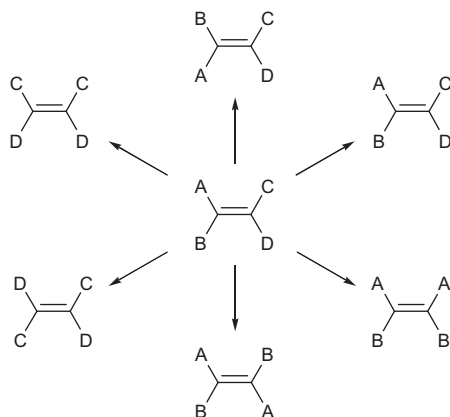
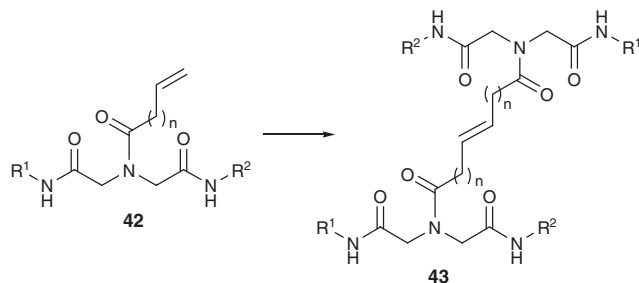


Fig. 2.10-6. X-MET on a single olefin with itself can produce five additional compounds along with the original olefin.



Scheme 2.10-13

2.10.3

Polymer-Supported Metathesis Catalysts

One highly desirable reagent for parallel synthesis would be a polymer-bound olefin metathesis catalyst. Such organometallic complexes have the potential to eliminate ruthenium byproducts, lessen or eliminate the need for chromatography, and offer the possibility of reusability. Figure 2.10-7 illustrates a selection of the polymer-supported catalysts that have been reported to date.

The first report of a polymer-supported metathesis catalyst was by Grubbs in 1995. While complex **44** did metathesize *cis*-2-pentene and polymerize norbornene, the activity was much lower than the parent system [55]. The next advance came in 1999, when Barrett reported a so-called “boomerang” catalyst **45** [56]. As the name implies, it is believed that the active catalyst becomes detached from the vinyl polystyrene support during the initial metathesis event and reattaches itself when all of the RCM substrate has been consumed. The Barrett group has since reported a recyclable “boomerang” catalyst derived from catalyst **1c** [57]. In addition there have been several other reports of polystyrene-bound catalysts reported by Nolan [58], Mol [59], and Blechert [60].

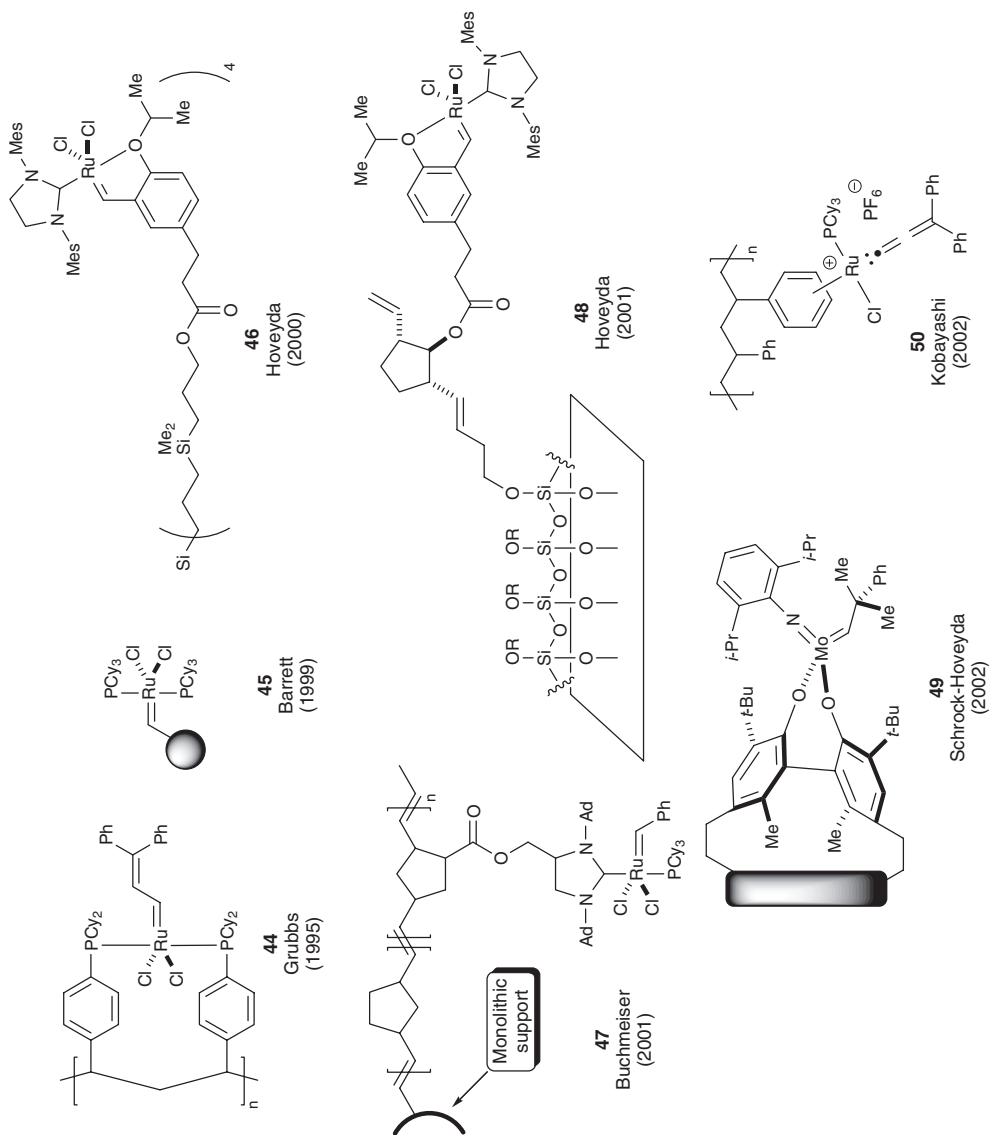


Fig. 2.10.7. Polymer-supported metathesis catalysts and publication dates.

In 2000, Hoveyda reported the dendritic ruthenium catalyst **46** [61]. This catalyst was highly active in both RCM and ROM/RCM reactions and could be easily recovered through chromatography. The Hoveyda group has since reported sol-gel-supported catalyst **48** [62]. These catalysts were produced from commercially available glass monolithic discs; the reaction mixtures were conveniently isolated using a Pasteur pipette. Ru content of the crude samples was very low (0.04–0.06% by mass), and the catalysts were recycled up to 12 times. A polystyrene version of the Hoveyda complex was also reported by the Blechert [63], Grela [64], and Dowden [65] groups. In addition, the Blechert group has shown that the Hoveyda complex can also be attached to a PEG-based support and utilized for RCM and X-MET reactions in water and methanol [66].

Buchmeiser has reported two strategies to attach catalyst **1c** to a polymeric support. The first utilized ROMP to generate a monolithic support, which was further modified for attachment of the catalyst in order to form **47** [67]. The second strategy employed a silica-based support [68]. There has even been a report of a metathesis catalyst embedded within a zeolite [69]. Schrock and Hoveyda have also reported that polystyrene-based complex **49** can be used for enantioselective RCM and ROM/X-MET reactions [70]. Last, but not least, the polystyrene-bound arene ruthenium complex **50** has been reported by Kobayashi to be an active catalyst for RCM, hydrogenation, and other cyclization reactions [71]. All of these systems show promise as tools for parallel synthesis.

2.10.4

ROMP-Based Strategies

The demand for new technologies in library synthesis is ever increasing. Two areas that have seen rapid growth in recent years are developments in soluble [72] and insoluble [73] polymer-supported reagents and soluble supports [74]. If inroads are to be made in these areas, a few improvements should be addressed concerning: (1) the traditionally low loading associated with polymer-supported reagents and supports, typically 1–1.5 mmol g⁻¹; (2) reaction kinetics; (3) ease of purification; (4) the yield and purity of reaction products; (5) the reagent and/or support that should be readily synthesized from easily obtainable and cheap starting materials; and (6) the ease with which the technique can be implemented without specialized training or requiring specialized equipment. One technique that is particularly well suited to address these issues is ring-opening metathesis polymerization (ROMP). This review will discuss the developments made to address issues 1–4. First, a few words must be said about ROMP in general that make it particularly well-suited to address points 5 and 6.

As a polymerization technique, ROMP is selective for strained, cyclic olefins. Typically, the monomers employed are norbornene- or 7-oxonorbornene-based. As such, they can easily be prepared from a Diels-Alder reaction between cyclopentadiene or furan and a suitable dienophile or from palladium-catalyzed reac-



Fig. 2.10-8. Typical cross-linking agents used in ROM polymerization.

tions involving norbornadiene. Because of the low cost and ready availability of these starting materials, monomers can be constructed in large scale.

ROMP is also a very “organic chemist-friendly” polymerization technique. The catalysts are commercially available and are no different from those used to perform the familiar ring-closing metathesis. The only difference is that ROM polymerizations are typically performed at higher concentrations (0.1 M) than an RCM (0.01–0.05 M). No special equipment is required to perform a ROM polymerization. A polymerization can be carried out in flasks or screw-cap vials, inside or outside of a glove box. Reaction scale is not an issue either, as polymerizations can be conducted on as little as 10–20 mg to multi-gram or kilogram scales.

There are a few other relevant characteristics of ROMP that should be addressed before continuing. First, the length of the ROM polymer can have a profound effect on its solubility. Typically, shorter oligomers will remain soluble in common reaction solvents (CH_2Cl_2 , CHCl_3 , THF, DMF) yet can often be precipitated from methanol. The polymer length is conveniently controlled through the amount of catalyst employed for the polymerization; more catalyst will produce shorter oligomers, while less catalyst will produce longer oligomers. Because the initiation rate is similar to the propagation rate, 10 mol% of catalyst (10:1 monomer:catalyst) will produce mainly 10-mers, 5 mol% of catalyst (20:1 monomer:catalyst) will produce mainly 20-mers, etc. (see volume 3) It is also possible to control the solubility of the ROM polymers through the judicious use of cross-linking agents (Figure 2.10-8). ROM polymers constructed using cross-linkers typically result in insoluble gels that retain swelling properties analogous to those of traditional solid-phase resins.

This review will be focused on ROMP techniques that have been developed specifically for applications in library synthesis or to aid in purification. These techniques include Barrett’s ROMPgels, soluble ROMP reagents and solution-phase ROMP methods, and soluble ROM supports. There have been reports of ROM polymers being designed as ligands for solution-phase catalysis, and these will also be briefly mentioned here.

2.10.4.1

ROMPgel Reagents

The first ROMPgel reagent was reported in 1999 by Barrett. Since that time his group has published numerous reports of ROMPgels that have the potential to be utilized in library construction. He has also recently compiled an extensive review on the utility of ROMP in library synthesis [75].

In general terms, the ROMPgel reagents developed by Barrett are ideal for

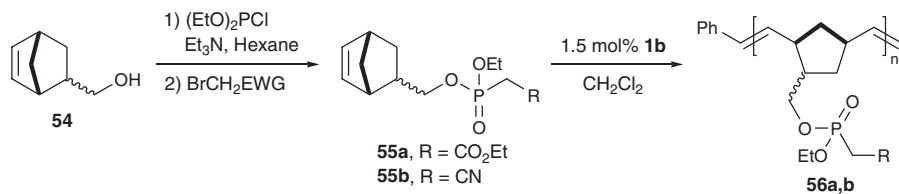
chromatography-free library synthesis. Because they are insoluble, swellable gels, a simple filtration of the reaction mixture through a short plug of Celite or silica will remove the polymer-bound reagents/byproducts from the desired products. One should keep in mind that this filtration is nothing more than a solid-phase extraction (SPE), as the column is short and only one fraction is collected. There should be no concern about ruthenium contamination, as all of the polymerizations are terminated with ethyl vinyl ether (EVE) upon complete consumption of monomer units. This technique also allows one to control the solubility properties through the use of cross-linking agents. Barrett's group has mainly concerned itself with insoluble ROM polymers; thus, the addition of cross-linking agents has mainly been used to ensure that the generated polymers are insoluble. Examples will be presented later in this report in which soluble ROM polymers were desired and no cross-linking agents were deployed.

Horner-Emmons reactions

Barrett's first example of the utility of ROMPgel reagents was demonstrated in the Horner-Emmons reaction [76]. While the Horner-Emmons reaction eliminates the traditional Wittig byproduct (i.e., Ph_3PO) by converting it into a water-soluble phosphate, this solution is still not readily amenable to combinatorial chemistry and library generation, as it would be more convenient to simply filter away the reaction byproduct. To reach this goal, Barrett constructed ROMPgel **56a,b** (Scheme 2.10-14). This would allow the phosphate byproduct and any unused phosphonate to be simply filtered away from the newly generated olefin products.

Monomeric phosphonate **55a,b** was obtained in excellent yield starting from commercially available 5-norbornene-2-methanol (**54**). Phosphonate **55a,b** was then polymerized using 1.5 mol% **1b**, followed by quenching of the polymerization with EVE. Because no cross-linker was utilized in this case, the loading of polymer **56a,b** is equal to that of the original monomer (i.e., 3.3 mmol g^{-1}) [76].

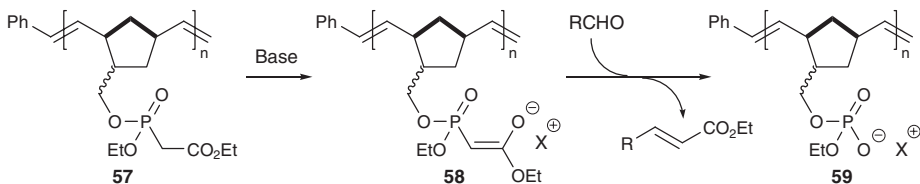
Two different conditions were found to be effective for the Horner-Emmons reaction: (1) pre-treating the ROMPgel with LHMDs (4 equivalents), followed by removal of excess base by filtration and washing, before addition of the aldehyde; and (2) utilizing tetramethylguanidine (TMG) or *tert*-butyltetramethylguanidine (Barton's base) in the presence of the aldehyde. While little difference was observed among the three bases, it was determined that Barton's base was the most general. In all cases, the reaction between ROMPgel **56a** and various aldehydes proceeded in high yield (>80%) and purity (>95%) and after filtration and evaporation of the



Scheme 2.10-14

solvent gave exclusively the *trans* olefin. ROMPgel **56b** also provided the olefins in high yield (>85%) and purity (>95%); however, the *E:Z* ratio varied from 70:30 to 100:0 [76].

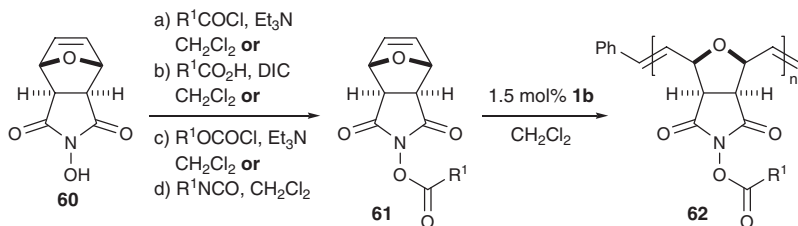
The success of filtration alone being sufficient for the purification of the olefin products rests on the ion pairing that results after the reaction is completed (Scheme 2.10-15). While Barton's base generates small amounts of **58** in solution, after the reaction the resulting phosphate **59** is ion paired with the protonated form of the base, sequestering it from solution. In addition, Barton's base is volatile enough that any excess base not washed from the product can be removed through simple evaporation [76].



Scheme 2.10-15

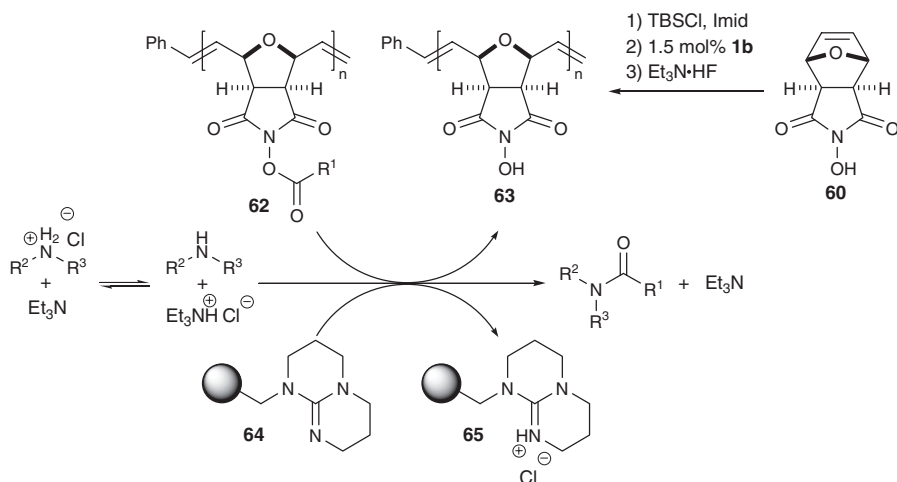
Acylation reactions

General acylation reactions Barrett next applied the ROMPgel technology in the area of acylation reactions. This was accomplished through the development of a ROMPgel-supported *N*-hydroxysuccinimide to serve as an acyl transfer agent. Commercially available monomer **60** was initially acylated by one of three methods: (1) reaction with an acid chloride or chloroformate, (2) di-isopropyl carbodiimide (DIC) coupling with a carboxylic acid, or (3) reaction with an isocyanate (Scheme 2.10-16). The resulting monomer **61** was then polymerized with 1.5 mol% **1b** and the polymerization was quenched with EVE to yield ROMPgel **62** [77].



Scheme 2.10-16

ROMPgel **62** was found to acylate a variety of amines with high yields (most >90%) and purity (>95%). Amine hydrochloride salts could also be used when triethylamine was employed as a proton shuttle and resin-supported base P-TBD (**64**) was used as a proton sink (Scheme 2.10-17). This allows for the HCl to be shuttled onto the solid-phase resin and subsequently filtered away at the end of

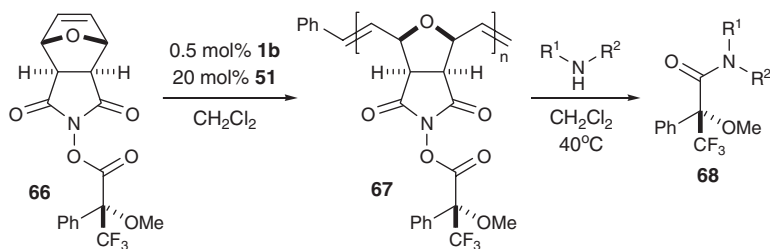


Scheme 2.10-17

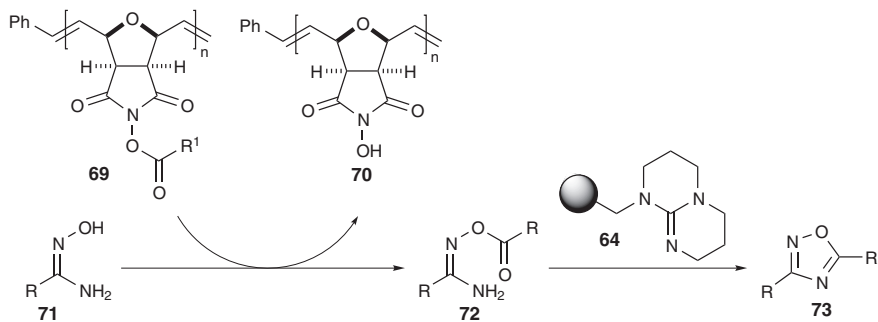
the reaction as **65**. The triethylamine employed is then removed simply by evaporation [77].

At the conclusion of the reaction, ROMPgel **63** can be collected and reused in other acylation reactions. Polymer **63** must first be treated with ammonia, after which it can be acylated by any of the methods mentioned previously to regenerate **62** for use in subsequent acylation reactions without any cross-contamination. A synthesis of ROMPgel **63** directly from **60** was also reported. Again, because no cross-linking agents were used to synthesize **63**, the loading is essentially the same as the monomer itself (5.5 mmol g⁻¹) [77].

Mosher amide formation This ROMPgel-supported *N*-hydroxysuccinimide strategy has also been applied in the synthesis of Mosher amides (Scheme 2.10-18). Monomer **66** was synthesized via DIC coupling between the Mosher acid and **60**. The polymerization was conducted with 0.5 mol% **1b** and 20 mol% **51** as a cross-linking agent and terminated with EVE to yield **67**. The low catalyst load and cross-linker were necessary in order to get a sufficiently insoluble polymer. Because of the inhomogeneity of ROMPgel **67**, the loading was lower than before (2.1 mmol g⁻¹) [78].



Scheme 2.10-18



Scheme 2.10-19

ROMPgel **67** was then treated with 0.8 equivalent of various chiral amines to afford Mosher amides **68** in high yield (80–94%) and >95% purity. Primary and secondary amines, as well as α -amino esters, reacted without difficulty. The reaction also proved to be chemoselective, as the amides were formed preferentially in the presence of alcohol moieties. The authors also claim that the reaction can be performed within an NMR tube, thus allowing for the direct determination of enantiomeric excess without isolation of the amide [78].

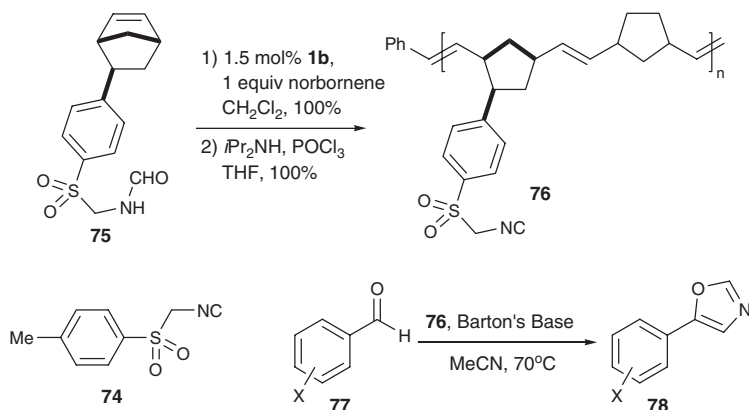
Oxadiazole formation This acylation strategy was also applied to the synthesis of a small library of 1,2,4-oxadiazoles (Scheme 2.10-19). In order to obtain sufficiently insoluble ROMPgels **69**, the corresponding monomers were polymerized with 1.5 mol% **1b** and 20 mol% **52** as a cross-linker. The loading of these cross-linked ROMPgels ranged from 2.39 to 3.74 mmol g⁻¹ [79].

The generated ROMPgels **69** were then treated with an assortment of amidoximes **71** in the presence of P-TBD (**64**). The initial reaction between **69** and **71** produced the acylated, non-polymer-bound species **72**. Cyclization then proceeded in the presence of **64** to ultimately yield **73**, which was isolated by simple filtration in 77–94% yield and >95% purity [79].

Tosmic reagent

One particularly useful reagent for heterocycle synthesis is the Tosmic reagent **74**. Although this reaction has shown wide use for the preparation of a range of different heterocycles, chromatography has often been required to obtain adequately pure reaction products. While a number of resin-based approaches to this problem have been attempted, all proved to be less than satisfactory. This prompted Barrett and coworkers to develop ROMPgel-based Tosmic reagent **76** and demonstrate its utility in the synthesis of a small library of oxazoles.

Monomeric Tosmic precursor **75** was synthesized in five steps and then polymerized with 1.5 mol% **1b** and 1 equivalent of norbornene (Scheme 2.10-20). The ROMPgel was then dehydrated to the isonitrile with POCl₃ and *i*Pr₂NH to yield ROMPgel **76** with a load capacity of 2.7 mmol g⁻¹. The monomeric isonitrile was also prepared, but it failed to polymerize [80].



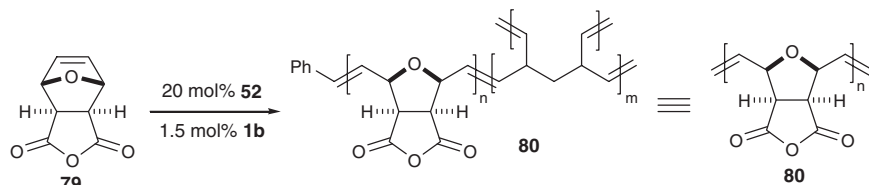
Scheme 2.10-20

With ROMPgel **76** in hand, the synthesis of a small oxazole library was attempted. Twelve aldehydes were heated with ROMPgel **76** in the presence of Barton's base to afford the corresponding oxazoles **78** in moderate to high yields (46–90%). Most of the products were isolated in >95% purity with two of the members, starting from benzaldehyde and *p*-methoxybenzaldehyde, being recovered in 90% and 66% purity, respectively. Both of these aldehydes also proved to be somewhat problematic in terms of slow reaction rates and incomplete reactions [80].

Anhydride-based scavenger

Having reported a ROMPgel-supported electrophile, the Barrett group next attempted to construct a ROMPgel that would be able to scavenge excess amines or hydrazines from solution-phase reactions. To this end, the commercially available anhydride **79** was copolymerized with 1.5 mol% **1b** and 20 mol% **52** to produce ROMPgel **80** after termination with EVE (Scheme 2.10-21). This ROMPgel had an anhydride loading of 5.4 mmol g^{-1} [81].

The scavenging reactions were carried out by first reacting various isocyanates, isothiocyanates, acid chlorides, sulfonyl chlorides, chloroformates, or aldehydes with 3 equivalents of an amine or hydrazine. ROMPgel **80** (3 equivalents) was then added after a sufficient reaction time in order to scavenge the excess amine or hydrazine. In the cases where HCl was evolved during the reaction, polyvinylpyridine was added as a resin-bound base. It is important to realize that while ROMPgel



Scheme 2.10-21



81

82

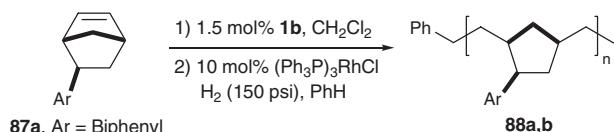
(Ionically
Scavenged)

(Covalently
Scavenged)

86a, R = H
86b, R = Me



84



Scheme 2.10-24

complete, the reaction product was filtered and evaporated to afford the homo-allylic alcohols in moderate to high yield (49–96%) and excellent purity (>95%) [82].

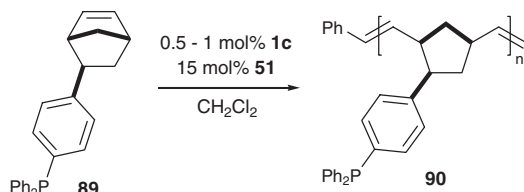
Arene-catalyzed lithiation reactions

Barrett and coworkers have also shown that ROMPgels are able to function in a catalytic role. This was first applied to arene-catalyzed lithiation reactions. Biphenyl- and naphthyl-containing monomers (**87a** and **87b**, respectively) were each polymerized with 1.5 mol% **1b**, and the resulting polymer backbone was subsequently hydrogenated with 10 mol% $(\text{Ph}_3\text{P})_3\text{RhCl}$, generating ROMPgels **88a,b** (Scheme 2.10-24) [83].

The ability of ROMPgels **88a,b** to catalyze the lithiation of chlorinated compounds was then examined. To this end, aliphatic and aromatic chlorides were treated with lithium metal, 10–20 mol% of ROMPgel **88a** or **88b**, and a suitable electrophile to trap the lithiated species (PhAc , PhCHO , or R_3SiCl) in THF at -78°C . After quenching the reaction, it was found that the trapped products were obtained in good yields (65–87%) and high purities (80–96%). ROMPgels **88a,b** were also employed in catalytic amounts (10 mol%) for the reductive cleavage of benzyl and allyl ether-protecting groups. The cleavage of these ethers proceeded in good yields (71–89%) and high purity (80–96%). The authors were also able to show that silyl ethers were not affected by this deprotection method [83].

Supported triphenylphosphine

One reagent that has been utilized in a wide array of reactions is triphenylphosphine. Unfortunately, either the reagent itself or its phosphine oxide byproduct can often be difficult to separate from reaction products. Because of these problems, Barrett and coworkers designed a ROMPgel-supported triphenylphosphine (Scheme 2.10-25). Phosphine monomer **89** was synthesized in two steps from norbornadiene and subsequently polymerized with 0.5–1.0 mol% **1c** and 15 mol%



Scheme 2.10-25

of the cross-linking agent **51**. This resulted in ROMPgel **90** with a phosphine load of 2.5 mmol g⁻¹ [84]. The authors then applied this ROMPgel in typical reactions involving triphenylphosphine.

ROMPgel **90** was examined in four different reactions. First, it was shown that **90** was able to convert alcohols into halides in the presence of CCl₄, CBr₄, or I₂. It was found that alkyl chlorides could be formed in high yield (89–100%) and >95% purity. Alkyl bromides and iodides could also be produced, though in lower yields. ROMPgel **90** was also employed for the reduction of ozonides, as well as for the isomerization of α,β -acetylenic esters to $\Delta^{2,4}$ -dienoates. Both of these reactions proceeded in nearly quantitative yield and with >95% purity. Finally, ROMPgel **90** was deployed for the Staudinger reaction. These examples proceeded in 87–100% yield and 90–98% purity [84].

2.10.4.2

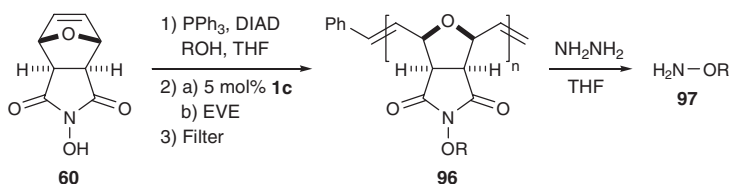
ROMP as a Purification Tool

Barrett and Hanson/Flynn have also shown that ROMP can be employed as a purification tool. This was accomplished by employing chemically tagged reagents [85]. The chemical tag should be inert towards reaction conditions yet allow for the selective and clean removal of the tagged reagent, product, and/or byproduct. In the following cases, the chemical tag is the norbornene ring system [86]. The norbornene ring system is ideal as a chemical tag as it is generally inert towards many reaction conditions, is generated readily through Diels-Alder chemistry, and can be readily polymerized through ROMP. ROMP is ideal as a polymerization method for purification purposes, as the technique can tolerate a wide range of functional groups, produces well-defined polymers, and will selectively polymerize only strained olefins.

Because of this selectivity, it may be possible in some cases to add a monomeric reagent or scavenger that is equipped with a norbornenyl tag. Once the reaction is complete, the excess tagged reagents and byproducts can be selectively removed through an *in situ* polymerization event. If this type of strategy is not feasible (i.e., reactants contain potentially reactive double bonds or functional groups that are not compatible with the metathesis catalysts), then it may be possible to polymerize the reagent or scavenger such that it remains soluble in typical reaction solvents. This usually can be accomplished by not using a cross-linking agent or by generating fairly short oligomers. Once the oligomer is formed, it can be isolated away from the metathesis catalyst by precipitation, and the collected polymer then can be used as a soluble polymer-bound reagent in solution phase reactions.

Barrett impurity annihilation

Barrett's approach at utilizing ROMP as a purification tool in the Mitsunobu reaction focused on selectively removing the impurities from the reaction products. This was accomplished by employing polystyrene-supported triphenylphosphine (**91**) and norbornenyl-tagged azodicarboxylate **92** (Scheme 2.10-26). After the reac-



Scheme 2.10-27

tion was complete, the polystyrene-supported triphenylphosphine oxide (**94**) was filtered away, leaving behind the Mitsunobu product and **93**. By utilizing **91**, not only was the removal of the phosphine oxide byproduct facilitated but also any unreacted **92** was removed in the form of the zwitterionic complex **95**. Once the polystyrene-supported byproducts were filtered, the reaction was treated with catalyst **1b** to polymerize the hydrazine byproduct **93**. In this case, the polymerization was not quenched with EVE, allowing the polymer to be precipitated with hexane and filtered away from the Mitsunobu products. This allowed for the ruthenium catalyst to be filtered away along with the polymer, due to the living nature of the polymerization. The reaction products were obtained in moderate to high yields (43–100%) and in high purities (86–97%) [87].

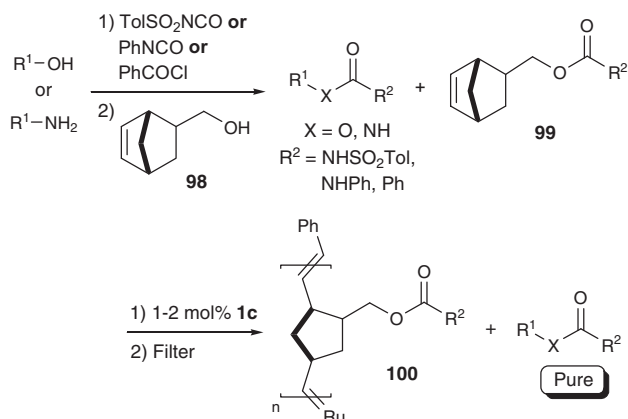
Capture-ROMP release

As an alternative to Barrett's approach, Hanson and coworkers decided to target the Mitsunobu product for selective removal (Scheme 2.10-27). This was accomplished by utilizing norbornenyl-tagged *N*-hydroxysuccinimide **60**. This tagged reagent served as the acidic component of the Mitsunobu reaction and was thus reacted with various alcohols under standard Mitsunobu conditions (Ph_3P , DIAD, THF). Because all of the reactants were small molecules, the reaction could be monitored using traditional techniques (GC, TLC). When the reaction was complete, the solvent was removed and replaced with CH_2Cl_2 . The Mitsunobu products were then polymerized with 5 mol% **1c**. When polymerization was complete, the polymerization was quenched with EVE, leaving the catalyst to be removed in solution. The polymerized reaction products **96** were then precipitated with methanol and filtered. By precipitating the polymer with methanol, the reaction byproducts (Ph_3PO , reduced DIAD, quenched catalyst) remained in solution, therefore selectively removing the desired products [88].

Once collected, **96** was then dissolved in THF and treated with anhydrous hydrazine to release the desired alkoxyamines **97**. It was found that the resulting polymer was actually water-soluble and therefore a simple ether/water extraction was enough to isolate product **97**. The alkoxyamines were isolated in good to high yields (58–97%) and good purities (63–91%). In all cases, the major impurity was residual hydrazine that could be azeotropically removed with toluene [88].

Scavenge-ROMP filter

Hanson, Flynn, and coworkers have applied *in situ* polymerization as a means of scavenging excess reagents from a reaction (Scheme 2.10-28). This was accom-



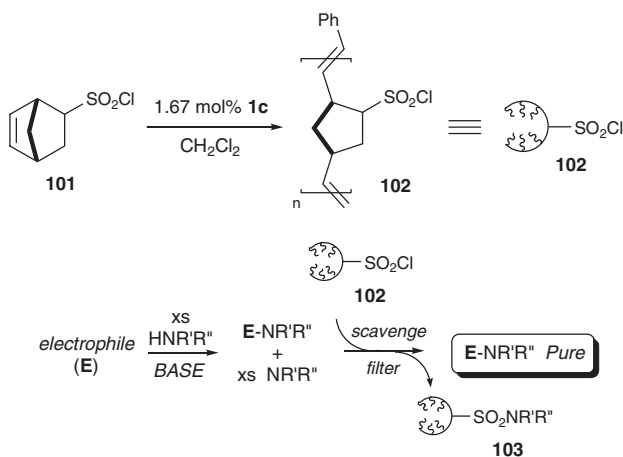
Scheme 2.10-28

plished by first reacting amines and alcohols with an excess of an electrophile (TsNCO, PhNCO, PhCOCl). Once the nucleophiles were completely consumed, as monitored by GC/TLC, norbornenyl-tagged alcohol **98** was added directly to the reaction mixture. When the electrophile was completely consumed, as monitored by GC/TLC, 1–2 mol% **1c** was added to polymerize the scavenged electrophile **99** and unreacted **98**. In this case the polymerization was not quenched. Instead, polymer **100** was precipitated and filtered away from the desired reaction products with the ruthenium catalyst still attached. Most products were isolated in high yields (>90%) and high purity (81–95%) [89].

Soluble oligomeric sulfonyl chloride

Hanson, Flynn, and coworkers have also shown that preformed, soluble oligomers can serve as scavenging agents. Sulfonyl chloride **101** was synthesized from cyclopentadiene and vinyl sulfonyl chloride and then polymerized with 1.67 mol% **1c** (Scheme 2.10-29). After quenching with EVE, polymer **102** was precipitated from ether, filtered, and isolated as a free-flowing powder that has a wide solubility profile (soluble in CH₂Cl₂, THF, and DMF; insoluble in MeOH, Et₂O, and EtOAc) [90]. The oligomer was then tested for its ability to scavenge amines after reaction with various electrophiles.

Benzoyl chloride, TsCl, and PhSO₂Cl were reacted with an excess of amines to form amides or sulfonamides. Once consumption of the electrophile was complete, the soluble **102** was added to scavenge the unreacted amines. When scavenging was complete, polymer **103** was precipitated with ethyl acetate and filtered. The resulting amides and sulfonamides were obtained in high yield (76–99%) and excellent purity (>90–99%). It should be noted that determining the amount of sulfonyl chloride added was facile, as no cross-linker was employed; therefore, the amount of polymer added is equivalent to the molecular weight of the monomer (5.2 mmol g⁻¹) [90].



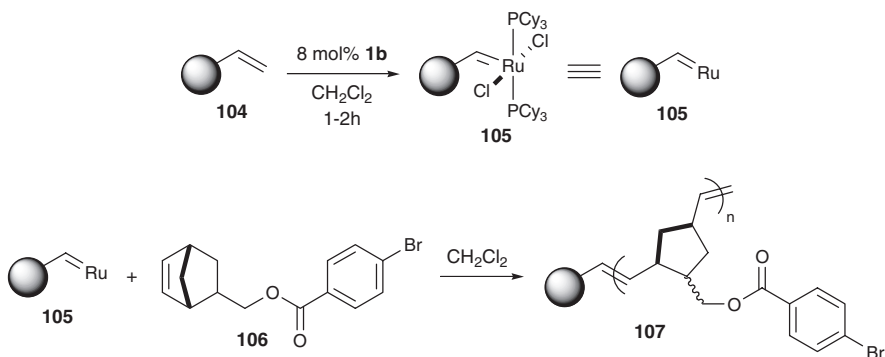
Scheme 2.10-29

2.10.4.3

ROMPspheres

One particularly interesting application of ROMP has been to solve a long-standing problem of traditional solid-phase supports, namely, the low load capacity. In essence, this approach uses ROMP to graft on more reactive units, thereby increasing the load capacity of the original resin. To accomplish this, Barrett and coworkers incubated vinyl polystyrene (**104**, 0.8 mmol g^{-1}) with 8 mol% **1b** to obtain polystyrene-bound ruthenium complex **105** (Scheme 2.10-30).

The incubation time was found to be critical in order to avoid backbiting on the resin and lowering the amount of resin-bound catalyst. Once isolated, complex **105** was treated with monomer **106**, followed by termination with EVE to yield ROMPsphere **107**. The authors found that the load capacity of the ROMPsphere could be varied simply by changing the ratio of **106** to **105**. A 4:1 ratio gave a loading of 2.52 mmol g^{-1} , while a ratio of 100:1 gave a loading of 3.03 mmol g^{-1} .



Scheme 2.10-30

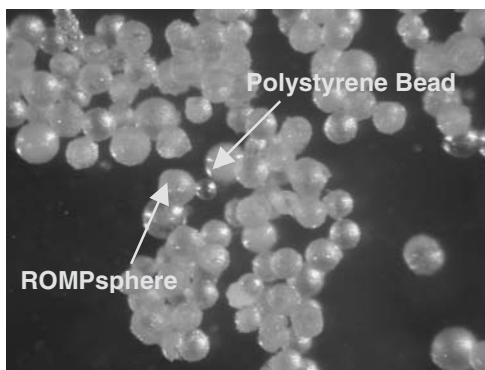
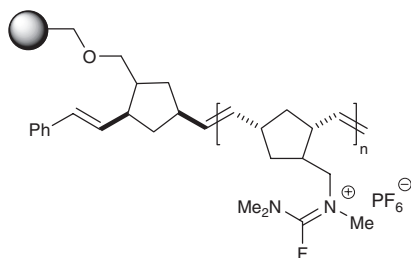


Fig. 2.10-9. Size comparison between vinyl polystyrene resin and ROMPsphere-supported formamidine peptide-coupling reagent [75].

The ROMPspheres so formed were found to be larger than the original vinyl polystyrene (Figure 2.10-9), and they still retained solvent-dependent swelling properties [91].

The ROMPspheres were then investigated for use in solid-phase reactions. The authors found that ROMPsphere **107** was a competent support for a palladium-catalyzed coupling between bromobenzoate **107** and an aryl zincate. Once the coupling reaction was finished, the resulting biaryl derivative could be cleaved from the resin with sodium methoxide [91].

2.10.4.4

ROM Polymers as Supports

One intriguing use of ROM polymers is their ability to function as soluble polymeric supports. The advantages ROM polymers have over more traditional soluble supports are threefold: (1) they are easy to prepare; (2) they have comparatively high loadings, as every monomer unit in the polymer has a functionalized unit; and (3) they can often be precipitated from methanol, a particular advantage at late stages when the cleaved scaffold is being removed from the support. The earliest reports of ROM polymers being utilized as soluble supports were in the area of ligand immobilization for catalysis. More recently, they have been successfully deployed as soluble supports for scaffold elaboration.

ROM supports for catalysts

Diethylzinc additions The first report of ROM polymers functioning as soluble polymeric supports for asymmetric catalysis was by the Bolm group. Homopolymers **108** and **109** (Figure 2.10-10) were synthesized in varying chain lengths and assayed for their ability to catalyze the reaction between diethylzinc and benzaldehyde. While the reaction catalyzed by the polymers required longer reaction times

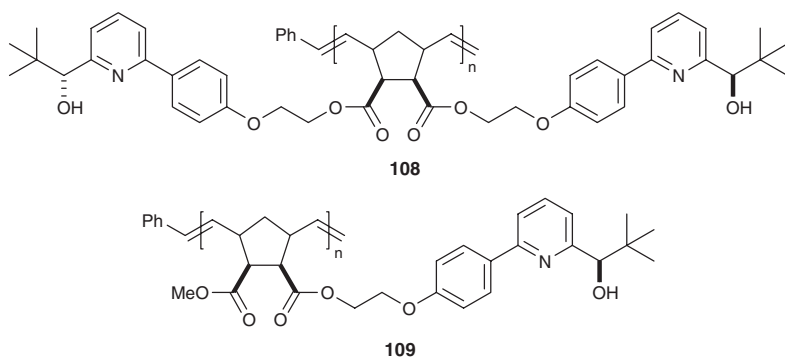


Fig. 2.10-10. ROM supported pyridinyl alcohols.

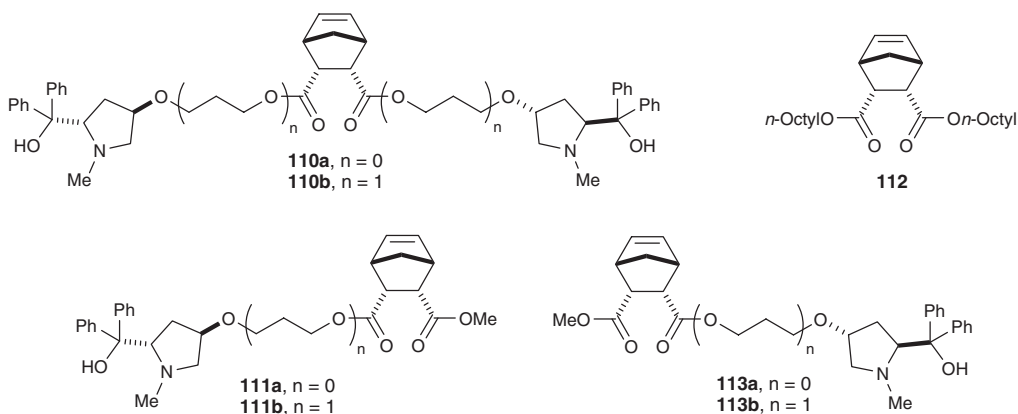


Fig. 2.10-11. ROM supported hydroxyproline derivatives.

than those of the individual monomers, the yields were comparable (48 h, 77–88% and 24 h, 72–89%, respectively). The enantiomeric excesses produced by the polymers (71–73%) were slightly lower than those produced by the individual monomers (79–83%). Varying the length of the polymers did not seem to have any effect on either yield or *ee* [92].

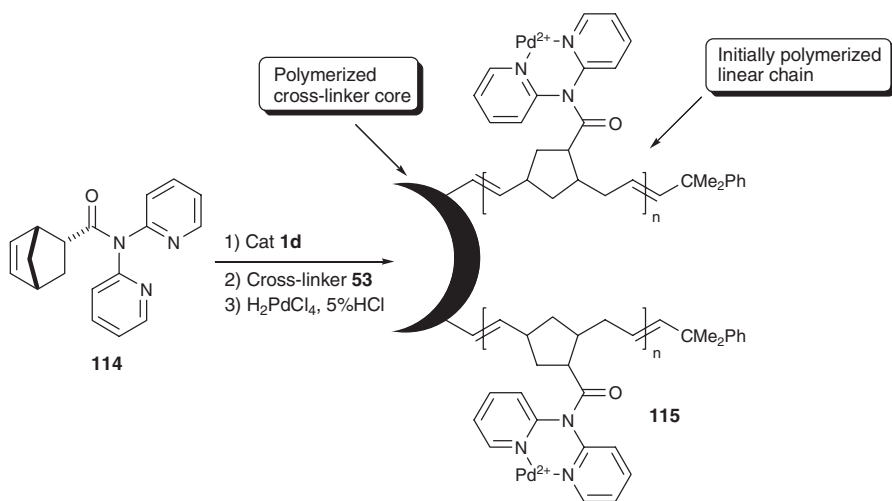
While the Bolm group was able to show that chain length does not appear to affect yield or *ee* in diethylzinc additions, they subsequently were able to show that the composition of the polymer backbone can have a very profound effect on *ee*. Monomers **110a,b** and **111a,b** were copolymerized with 0–8 equivalents of achiral monomer **112** (Figure 2.10-11) using 10 mol% **1b**, and the resulting homopolymers and random copolymers were assayed for their ability to catalyze the addition of diethylzinc to benzaldehyde. In general, the copolymers produced with 1 equivalent of **112** gave product in the highest *ee* (84–89% *ee*), depending on which chiral monomer was used. It should also be noted that these copolymers also resulted in higher *ee*'s than the monomers alone [93].

The dependence of *ee* on the backbone was further tested by altering the chirality elements of the monomers. Monomers **113a,b** were synthesized for this purpose.

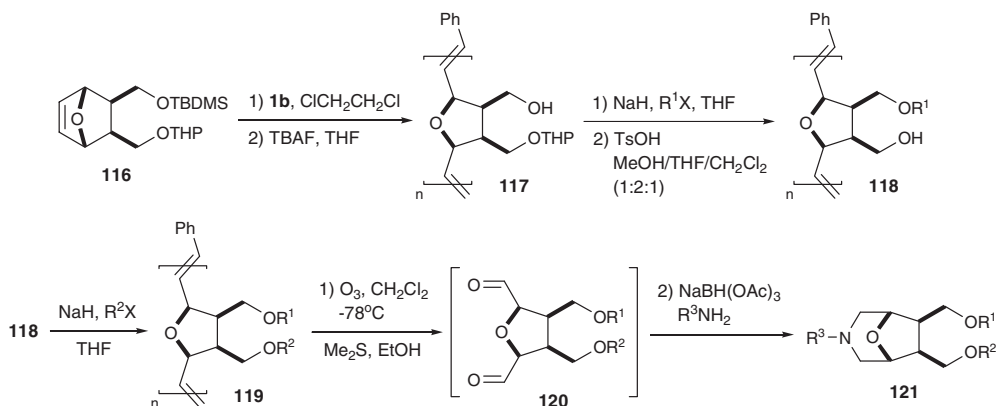
The catalytically active portion of **113a,b** has the same absolute stereochemistry as the catalytically active portion of **111a,b**; however, the absolute chirality of the norbornene ring has been altered. Homopolymers of **113a,b** and copolymers with 1 equivalent of **112** were synthesized and assayed as before. Surprisingly, the *ee*'s produced by both of the homopolymers (51% and 48%) and both of the copolymers (50% each) were significantly lower than the *ee*'s produced by the monomers alone (88% and 90%). The authors were able to explain these results as a combination of kinetic differences between the two diastereomers, as well as subtle structural differences that enhance or destroy the chiral environment [93].

Palladium-catalyzed reactions The Buchmeiser group has also used ROMP to generate supported ligands for catalysis, but with a different approach. Instead of producing soluble polymeric ligands, they used ROMP to construct an insoluble block copolymer resin. This was accomplished by first polymerizing monomer **114** with the Schrock catalyst (**1d**). Cross-linker **53** was added to the resulting linear living homopolymer. The resulting heterogeneous resin was then incubated with H_2PdCl_4 to give resin **115** (Scheme 2.10-31) [94, 95].

Resin **115** was then tested for its ability to participate in various palladium-catalyzed processes. Heck-type reactions among aryl iodides and styrene, vinyl ferrocene, and TMS-acetylene were found to proceed well with as little as 3×10^{-3} mol%, despite the heterogeneous conditions. In addition, aryl bromides and aryl chlorides were also found to participate in Heck-type reactions with styrene, although the couplings with aryl chlorides required the use of tetrabutylammonium bromide [94]. The heterogeneous catalyst was also found to catalyze the copolymerization of dibromobenzene and divinylbenzene [94, 96]. Additionally, the catalyst was shown to be modestly active in the palladium-catalyzed amination of



Scheme 2.10-31



Scheme 2.10-32

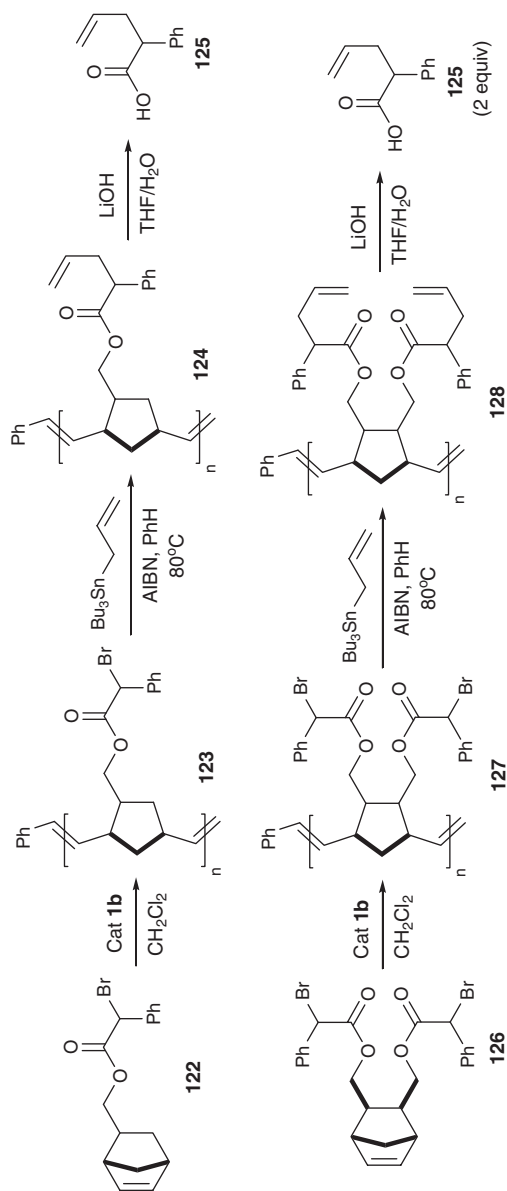
aryl bromides [94]. These and other similar resins have also been employed as catalysts for Heck, Suzuki, and Sonogashira-Hagihara couplings [97].

Soluble supports for scaffold elaboration

Vanishing polymeric support The first attempt at the utilization of ROM polymers as soluble supports, as shown in Scheme 2.10-32, was reported by Barrett and coworkers. Orthogonally protected diol **116** was polymerized with **1b**, followed by termination with EVE and precipitation with MeOH. The collected polymer was deprotected with TBAF to afford polymer **117**. Alkylation of the free alcohol was performed, followed by deprotection of the THP ether, yielding **118** that was alkylated again to give **119**. At each step to this point, the polymers were isolated either by precipitation from MeOH or as THF-insoluble precipitates [98].

The authors then treated polymer **119** with ozone, followed by Me_2S workup. This step effectively cleaved the polyolefin backbone to give bisaldehyde **120**, which was immediately subjected to reductive amination conditions to produce the bicyclic product **121** [98]. This example is important in that it demonstrated that ROM polymers could serve as soluble supports and could be cleanly isolated from reaction byproducts through precipitation. Furthermore, it offers an intriguing synthesis design element in that the polymer backbone can serve as a carbonyl-protecting group to be revealed at a key juncture in a synthetic sequence. This last point is significant in that 100% of the original monomer is utilized in the construction of the final product, eliminating the need to “throw away” the spent support once the synthesis is completed.

Free radical reactions on soluble ROM supports Enholm has since shown that soluble ROM supports can be used in free radical reactions despite the highly olefinated backbone. The first example of this began by polymerizing α -bromoester **122** with catalyst **1b** and quenching with EVE (Scheme 2.10-33). Polymer **123** was



Scheme 2.10-33

isolated by precipitation with MeOH and filtering. Polymer **123** was then treated with allyltributyltin and AIBN to give γ,δ -unsaturated ester **124**. The polymer could be precipitated away from the contaminating tin salts with methanol. Hydrolysis of the ester with LiOH afforded carboxylic acid **125**. Furthermore, the authors were able to show that diester **126** could also be used in a similar sequence to produce 2 equivalents of acid **125** without complication [99].

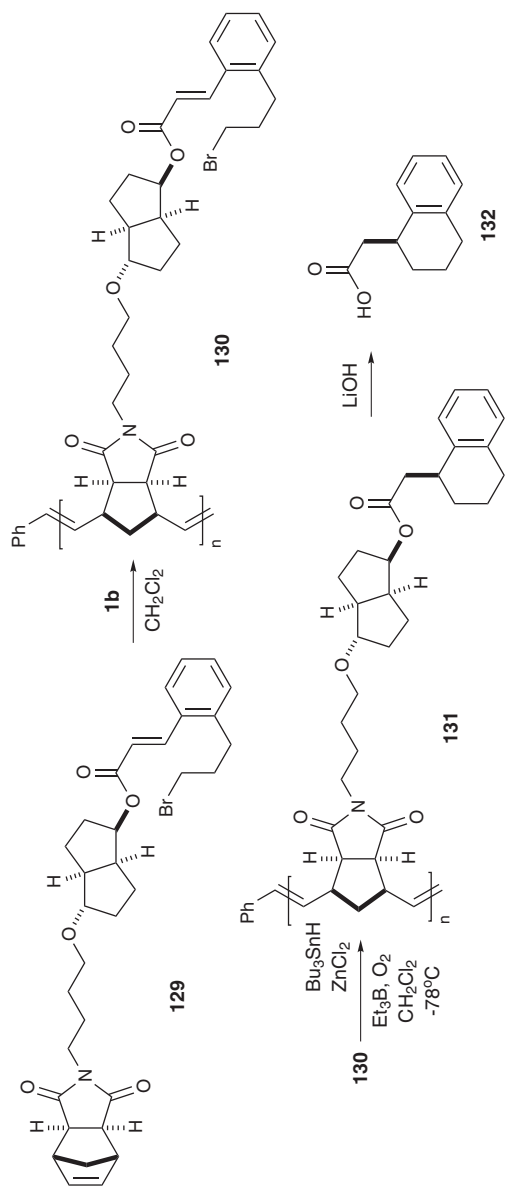
Enholm's group has since followed up this result by reporting the utility of soluble ROM supports in diastereoselective free radical reactions (Scheme 2.10-34). This was accomplished by embedding a chiral auxiliary within a ROM polymer. Enantiomerically pure monomer **129** was polymerized with catalyst **1b** and quenched with EVE to produce **130**, which was precipitated and filtered away from the terminated catalyst. Polymer **130** was then subjected to radical cyclization conditions to give **131**. Upon completion of the reaction, polymer **131** was precipitated away from the resulting tin salts with MeOH. Carboxylic acid **132** was then cleaved from the support with LiOH and isolated in >99% *ee* [100]. These examples are remarkable in that the ROM support did not interfere with the free radical reactions despite the highly olefinated nature of the backbone.

RCM on soluble ROM supports Hanson, Flynn, and coworkers have shown that the polyolefin backbone of ROM polymers is also compatible with RCM reactions (Scheme 2.10-35). Their entry into the soluble ROM supports was made by utilizing the capture-ROMP method they had previously developed [88, 89]. Monomer **133** was subjected to a Mitsunobu reaction with cinnamyl alcohol, and the crude reaction mixture was then treated with 5 mol% **1c** to polymerize the norbornenyl-tagged monomers. Quenching of the polymerization with EVE followed by precipitation of the oligomers with methanol provided oligomer **134** free of Mitsunobu byproducts. In this sequence, the terminal phenyl group in **134** provided sufficient protection of the double bond during the ROM polymerization event. Allylation of the soluble oligomer **134** was performed in DMF and the resulting oligomer **135** was precipitated from water, thereby removing the inorganic salts and DMF [101].

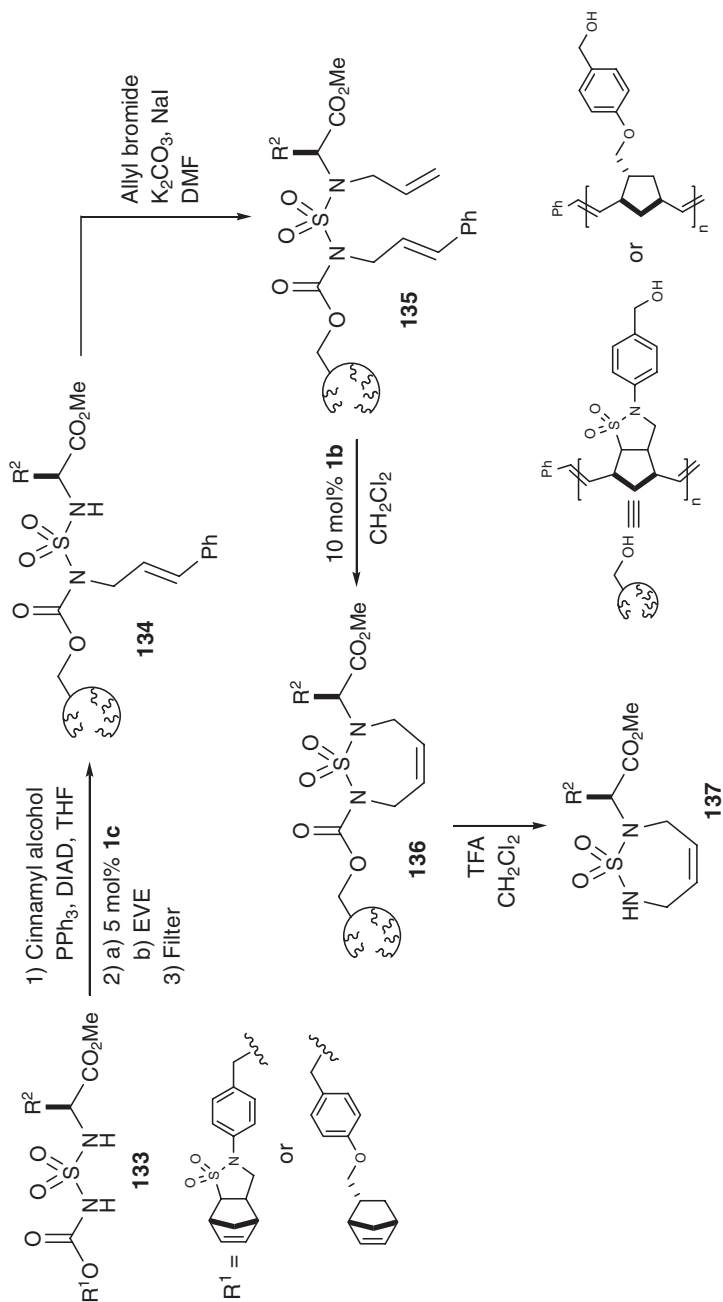
Oligomer **135** was then dissolved in CH₂Cl₂ and treated with 10 mol% **1b** to effect the RCM reaction to **136**. Because ROM supports **135** and **136** were soluble in CDCl₃, the RCM reaction could be conveniently monitored in solution by following the disappearance of the terminal CH₂ of **135** via DEPT NMR. Once RCM was complete, the ROM support **136** was precipitated from methanol and subsequently treated with TFA to cleave sulfamide **137** [101].

2.10.5 Conclusions

In conclusion, this chapter has outlined the rapidly developing area of metathesis in combinatorial chemistry. Thus far, RCM, ROM, X-MET, and ROMP have all played a prominent role in library development. The continued development of well-defined, homogeneous catalysts can only add to the growing utility of this



Scheme 2.10-34



Scheme 2.10:35

enabling technology, and thus its full potential waits to be seen. As a final note, it is the authors' hope that this chapter serves as a guide for the continued development of new metathesis-based technologies for use in combinatorial chemistry and organic synthesis.

Acknowledgements

The authors would like to thank the National Science Foundation (NSF Career 9984926), the National Institutes of Health (National Institute of General Medical Sciences, RO1-GM58103), and Neogenesis Pharmaceuticals, Inc., for generous support of our program. In addition, we would like to thank the ACS Division of Organic Chemistry Nelson J. Leonard Fellowship sponsored by Organic Syntheses, Inc., for supporting A. M. H. The authors also gratefully acknowledge Prof. Anthony G. M. Barrett for supplying the photo for Figure 2.10-9, as well as Materia, Inc., for many helpful discussions.

References

- SCHUSTER, M.; PERNERSTORFER, J.; BLECHERT, S. *Angew. Chem. Int. Ed.* **1996**, 35, 1979–1980.
- PERNERSTORFER, J.; SCHUSTER, M.; BLECHERT, S. *Synthesis* **1999**, 138–144.
- BREED, P. G.; RAMSDEN, J. A.; BROWN, J. M. *Can. J. Chem.* **2001**, 79, 1049–1057.
- MILLER, S. J.; BLACKWELL, H. E.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1996**, 118, 9606–9614.
- REICHWEIN, J. F.; LISKAMP, R. M. J. *Eur. J. Org. Chem.* **2000**, 2335–2344.
- (a) KRUIJTZER, J. A. W.; LISKAMP, R. M. J. *Tetrahedron Lett.* **1995**, 39, 6969–6972. (b) KRUIJTZER, J. A. W.; HOFMEYER, L. J. F.; HEERMA, W.; VERSLUIS, C.; LISKAMP, R. M. J. *Chem.–Eur. J.* **1998**, 4, 1570–1580.
- SCHMIEDEBERG, N.; KESSLER, H. *Org. Lett.* **2002**, 4, 59–62.
- STYMIEST, J. L.; MITCHELL, B. F.; WONG, S.; VEDERAS, J. C. *Org. Lett.* **2003**, 5, 47–49.
- REICHWEIN, J. F.; WELS, B.; KRUIJTZER, J. A. W.; VERSLUIS, C.; LISKAMP, R. M. J. *Angew. Chem. Int. Ed.* **1999**, 38, 3684–3687.
- KOIDE, K.; FINKELSTEIN, J. M.; BALL, Z.; VERDINE, G. L. *J. Am. Chem. Soc.* **2001**, 123, 398–408.
- TANG, Q.; WAREING, J. R. *Tetrahedron Lett.* **2001**, 42, 1399–1401.
- LEE, D.; SELLO, J. K.; SCHREIBER, S. L. *Org. Lett.* **2000**, 2, 709–712.
- VARRAY, S.; LAZARO, R.; MARTINEZ, J.; LAMATY, F. *Eur. J. Org. Chem.* **2002**, 2308–2316.
- VAN MAARSEVEEN, J. H.; DEN HARTOG, J. A. J.; ENGELEN, V.; FINNER, E.; VISSER, G.; KRUSE, C. G. *Tetrahedron Lett.* **1996**, 37, 8249–8252.
- VEERMAN, J. J. N.; VAN MAARSEVEEN, J. H.; VISSER, G. M.; KRUSE, C. G.; SCHOEMAKER, H. E.; HIEMSTRA, H.; RUTJES, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 2583–2589.
- PERNERSTORFER, J.; SCHUSTER, M.; BLECHERT, S. *Chem. Commun.* **1997**, 1949–1950.
- SASMAL, S.; GEYER, A.; MAIER, M. E. *J. Org. Chem.* **2002**, 67, 6260–6263.
- PISCOPIO, A. D.; MILLER, J. F.; KOCH, K. *Tetrahedron Lett.* **1997**, 38, 7143–7146.
- PISCOPIO, A. D.; MILLER, J. F.; KOCH, K. *Tetrahedron Lett.* **1998**, 39, 2667–2670.
- PISCOPIO, A. D.; MILLER, J. F.; KOCH, K. *Tetrahedron* **1999**, 55, 8189–8198.
- BROWN, R. C. D.; CASTRO, J. L.; MORIGGI, J.-D. *Tetrahedron Lett.* **2000**, 41, 3681–3685.
- NICOLAOU, K. C.; WINSSINGER, N.; PASTOR, J.; NINKOVIC, S.; SARABIA, F.; HE, Y.; VOURLUMIS, D.; YANG, Z.; LI,

- T.; GIANNAKAKOU, P.; HAMEL, E. *Nature* **1997**, 387, 268–272.
- 23 NICOLAOU, K. C.; VOURLOUMIS, D.; LI, T.; PASTOR, J.; WINSSINGER, N.; HE, Y.; NINKOVIC, S.; SARABIA, F.; VALLBERG, H.; ROSCHANGAR, F.; KING, N. P.; FINLAY, M. R. V.; GIANNAKAKOU, P.; VERDIER-PINARD, P.; HAMEL, E. *Angew. Chem. Int. Ed.* **1997**, 36, 2097–2103.
- 24 PETERS, J. U.; BLECHERT, S. *Synlett* **1997**, 348–350.
- 25 KNERR, L.; SCHMIDT, R. R. *Synlett* **1999**, 1802–1804.
- 26 KNERR, L.; SCHMIDT, R. R. *Eur. J. Org. Chem.* **2000**, 2803–2808.
- 27 BIAGINI, S. C. G.; GIBSON, S. E.; KEEN, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485–2500.
- 28 CHANG, S.; NA, Y.; SHIN, H. J.; CHOI, E.; JEONG, L. S. *Tetrahedron Lett.* **2002**, 43, 7445–7448.
- 29 RUDDICK, C. L.; HODGE, P.; COOK, A.; MCRIENER, A. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 629–637.
- 30 BLACKWELL, H. E.; CLEMONS, P. A.; SCHREIBER, S. L. *Org. Lett.* **2001**, 3, 1185–1188.
- 31 CONDE-FRIEBOES, K.; ANDERSEN, S.; BREINHOLT, J. *Tetrahedron Lett.* **2000**, 41, 9153–9156.
- 32 CUNY, G. D.; CAO, J.; HAUSKE, J. R. *Tetrahedron Lett.* **1997**, 38, 5237–5240.
- 33 CAO, J.; CUNY, G. D.; HAUSKE, J. R. *Molecular Diversity* **1998**, 3, 173–179.
- 34 For an excellent review on ruthenium catalyzed enyne metathesis, see: POULSEN, C. S.; MADSEN, R. *Synthesis* **2003**, 1–18.
- 35 SCHUSTER, M.; BLECHERT, S. *Tetrahedron Lett.* **1998**, 39, 2295–2298.
- 36 SCHURER, S. C.; BLECHERT, S. *Synlett* **1998**, 166–168.
- 37 SCHURER, S. C.; BLECHERT, S. *Synlett* **1999**, 1879–1882.
- 38 HEERDING, D. A.; TAKATA, D. T.; KWON, C.; HUFFMAN, W. F.; SAMANEN, J. *Tetrahedron Lett.* **1998**, 39, 6815–6818.
- 39 ANDRADE, R. B.; PLANTE, O. J.; MELEAN, L. G.; SEEBERGER, P. H. *Org. Lett.* **1999**, 1, 1811–1814.
- 40 MELEAN, L. G.; HAASE, W.-C.; SEEBERGER, P. H. *Tetrahedron Lett.* **2000**, 41, 4329–4333.
- 41 SCHUSTER, M.; LUCAS, N.; BLECHERT, S. *Chem. Commun.* **1997**, 823–824.
- 42 HAMILTON, D. G.; FEEDER, N.; TEAT, S. J.; SANDERS, J. K. M. *New J. Chem.* **1998**, 22, 1019–1021.
- 43 CARDULLO, F.; CALAMA, M. C.; SNELLINK-RUEL, B. H. M.; WEIDMANN, J. L.; BIELEJEWSKA, A.; TIMMERMAN, P.; REINHOUTD, D. N.; FOKKENS, R.; NIBBERING, N. M. M. *Chem. Commun.* **2000**, 367–368.
- 44 GIGER, T.; WIGGER, M.; AUDETAT, S.; BENNER, S. A. *Synlett* **1998**, 688–691.
- 45 NICOLAOU, K. C.; HUGHES, R.; CHO, S. Y.; WINSSINGER, N.; LABISCHINSKI, H.; ENDERMANN, R. *Chem.–Eur. J.* **2001**, 7, 3824–3843.
- 46 BRAENDLI, C.; WARD, T. R. *Helv. Chim. Acta* **1998**, 81, 1616–1621.
- 47 PLETTENBURG, O.; MUI, C.; BODMER-NARKEVITCH, V.; WONG, C.-H. *Adv. Synth. Catal.* **2002**, 344, 622–626.
- 48 GIERASCH, T. M.; CHYTL, M.; DIDIUK, M. T.; PARK, J. Y.; URBAN, J. J.; NOLAN, S. P.; VERDINE, G. L. *Org. Lett.* **2000**, 2, 3999–4002.
- 49 HARRISON, B. A.; VERDINE, G. L. *Org. Lett.* **2001**, 3, 2157–2159.
- 50 For use of temporary silicon tethers with RCM, see: (a) EVANS, P. A.; MURTHY, V. S. *J. Org. Chem.* **1998**, 63, 6768–6769. (b) HOYE, T. R.; PROMO, M. A. *Tetrahedron Lett.* **1999**, 40, 4129–1432.
- 51 For use of temporary phosphorous tethers to produce 1,4 diamines, see: McREYNOLDS, M. D.; SPROTT, K. T.; HANSON, P. R. *Org. Lett.* **2002**, 4, 4673–4676.
- 52 BOGER, D. L.; CHAI, W.; OZER, R. S.; ANDERSON, C.-M. *Bioorg. Med. Chem. Lett.* **1997**, 7, 463–468.
- 53 BOGER, D. L.; CHAI, W. *Tetrahedron* **1998**, 54, 3955–3970.
- 54 BOGER, D. L.; CHAI, W.; JIN, Q. *J. Am. Chem. Soc.* **1998**, 120, 7220–7225.
- 55 NGUYEN, S. T.; GRUBBS, R. H. *J. Organomet. Chem.* **1995**, 497, 195–200.
- 56 AHMED, M.; BARRETT, A. G. M.; BRADDOCK, D. C.; CRAMP, S. M.; PROCOPIOU, P. A. *Tetrahedron Lett.* **1999**, 40, 8657–8662.

- 57 AHMED, M.; ARNAULD, T.; BARRETT, A. G. M.; BRADDOCK, D. C.; PROCOPIOU, P. A. *Synlett* **2000**, 1007–1009.
- 58 (a) JAFARPOUR, L.; NOLAN, S. P. *Org. Lett.* **2000**, 2, 4075–4078. (b) JAFARPOUR, L.; HECK, M.-P.; BAYLON, C.; LEE, H. M.; MIOSKOWSKI, C.; NOLAN, S. P. *Organometallics* **2002**, 21, 671–679.
- 59 NIECZYPOR, P.; BUCHOWICZ, W.; MEESTER, W. J. N.; RUTJES, F. P. J. T.; MOL, J. C. *Tetrahedron Lett.* **2001**, 42, 7103–7105.
- 60 SCHURER, S. C.; GESSLER, S.; BUSCHMANN, N.; BLECHERT, S. *Angew. Chem. Int. Ed.* **2000**, 39, 3898–3901.
- 61 GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, 122, 8168–8179.
- 62 KINGSBURY, J. S.; GARBER, S. B.; GIFTOS, J. M.; GRAY, B. L.; OKAMOTO, M. M.; FARRER, R. A.; FOURKAS, J. T.; HOVEYDA, A. H. *Angew. Chem. Int. Ed.* **2001**, 40, 4251–4256.
- 63 RANDL, S.; BUSCHMANN, N.; CONNON, S. J.; BLECHERT, S. *Synlett* **2001**, 1547–1550.
- 64 GRELA, K.; TRYZNOWSKI, M.; BIENIEK, M. *Tetrahedron Lett.* **2002**, 43, 9055–9059.
- 65 DOWDEN, J.; SAVOVIC, J. *Chem. Commun.* **2001**, 37–38.
- 66 CONNON, S. J.; BLECHERT, S. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1873–1876.
- 67 MAYR, M.; MAYR, B.; BUCHMEISER, M. R. *Angew. Chem. Int. Ed.* **2001**, 40, 3839–3842.
- 68 MAYR, M.; BUCHMEISER, M. R.; WURST, K. *Adv. Synth. Catal.* **2002**, 344, 712–719.
- 69 MELIS, K.; DE VOS, D.; JACOBS, P.; VERPOORT, F. *J. Mol. Catal. A* **2001**, 169, 47–56.
- 70 HULTZSCH, K. C.; JERNELIUS, J. A.; HOVEYDA, A. H.; SCHROCK, R. R. *Angew. Chem. Int. Ed.* **2002**, 41, 589–593.
- 71 AKIYAMA, R.; KOBAYASHI, S. *Angew. Chem. Int. Ed.* **2002**, 41, 2602–2604.
- 72 (a) BERGBREITER, D. E. *Chem. Rev.* **2002**, 102, 3345–3383. (b) VAN HEERBEEK, R.; KAMER, P. C. J.; VAN LEEUWEN, P. W. N. M.; REEK, J. N. H. *Chem. Rev.* **2002**, 102, 3717–3756.
- (c) DICKERSON, T. J.; REED, N. N.; JANDA, K. D. *Chem. Rev.* **2002**, 102, 3325–3343. (d) KIRSCHNING, A.; MONENSCHIN, H.; WITTENBERG, R. *Angew. Chem. Int. Ed.* **2001**, 40, 650–679.
- 73 (a) LEADBEATER, N. E.; MARCO, M. *Chem. Rev.* **2002**, 102, 3217–3273. (b) McNAMARA, C. A.; DIXON, M. J.; BRADLEY, M. *Chem. Rev.* **2002**, 102, 3275–3299. (c) LEY, S. V.; BAXENDALE, I. R.; BRUSOTTI, G.; CALDARELLI, M.; MASSI, A.; NESI, M. *Farmaco* **2002**, 57, 321–330. (d) EAMES, J.; WATKINSON, M. *Eur. J. Org. Chem.* **2001**, 1213–1224. (e) LEY, S. V.; BAXENDALE, I. R.; BREAM, R. N.; JACKSON, P. S.; LEACH, A. G.; LONGBOTTOM, D. A.; NESI, M.; SCOTT, J. S.; STORER, R. I.; TAYLOR, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195. (f) SHUTTLEWORTH, S. J.; ALLIN, S. M.; SHARMA, P. K. *Synthesis* **1997**, 1217–1239.
- 74 (a) HAAG, R. *Chem.–Eur. J.* **2001**, 7, 327–335. (b) KIRSCHNING, A.; MONENSCHIN, H.; WITTENBERG, R. *Angew. Chem. Int. Ed.* **2001**, 40, 650–679. (c) TOY, P. H.; JANDA, K. D. *Acc. Chem. Res.* **2000**, 33, 546–554. (d) GRAVERT, D. J.; JANDA, K. D. *Chem. Rev.* **1997**, 97, 489–509.
- 75 BARRETT, A. G. M.; HOPKINS, B. T.; KÖBBERLING, J. *Chem. Rev.* **2002**, 102, 3301–3324.
- 76 BARRETT, A. G. M.; CRAMP, S. M.; ROBERTS, R. S.; ZÉCRI, F. J. *Org. Lett.* **1999**, 1, 579–582.
- 77 BARRETT, A. G. M.; CRAMP, S. M.; ROBERTS, R. S.; ZÉCRI, F. J. *Org. Lett.* **2000**, 2, 261–264.
- 78 ARNAULD, T.; BARRETT, A. G. M.; HOPKINS, B. T.; ZÉCRI, F. J. *Tetrahedron Lett.* **2001**, 42, 8215–8217.
- 79 BARRETT, A. G. M.; CRAMP, S. M.; ROBERTS, R. S.; ZÉCRI, F. J. *Comb. Chem. High Throughput Screening* **2000**, 3, 131–138.
- 80 BARRETT, A. G. M.; CRAMP, S. M.; HENNESSY, A. J.; PROCOPIOU, P. A.; ROBERTS, R. S. *Org. Lett.* **2001**, 3, 271–273.
- 81 ARNAULD, T.; BARRETT, A. G. M.; CRAMP, S. M.; ROBERTS, R. S.; ZÉCRI, F. J. *Org. Lett.* **2000**, 2, 2663–2666.

- 82 ARNAULD, T.; BARRETT, A. G. M.; SEIFRIED, R. *Tetrahedron Lett.* **2001**, 42, 7899–7901.
- 83 ARNAULD, T.; BARRETT, A. G. M.; HOPKINS, B. T. *Tetrahedron Lett.* **2002**, 43, 1081–1083.
- 84 ÅRSTAD, E.; BARRETT, A. G. M.; HOPKINS, B. T.; KÖBBERLING, J. *Org. Lett.* **2002**, 4, 1975–1977.
- 85 For a general discussion on chemical tagging and phse-trafficking, see:
(a) FLYNN, D. L.; DEVRAJ, R. V.; NAING, W.; PARLOW, J. J.; WEIDNER, J. J.; YANG, S. *Med. Chem. Res.* **1998**, 8, 219–243. (b) FLYNN, D. L. *Med. Res. Rev.* **1999**, 19, 408–431.
- 86 For a review on norbornenyl-tags, see: FLYNN, D. L.; HANSON, P. R.; BERK, S. C.; MAKARA, G. M. *Curr. Opin. Drug Discov. Devel.* **2002**, 5, 571–579.
- 87 BARRETT, A. G. M.; ROBERTS, R. S.; SCHROEDER, J. *Org. Lett.* **2000**, 2, 2999–3001.
- 88 HARNED, A. M.; HANSON, P. R. *Org. Lett.* **2002**, 4, 1007–1010.
- 89 MOORE, J. D.; HARNED, A. M.; HENLE, J.; FLYNN, D. L.; HANSON, P. R. *Org. Lett.* **2002**, 4, 1847–1849.
- 90 MOORE, J. D.; HERPEL, R. H.; LICHTSINN, J. R.; FLYNN, D. L.; HANSON, P. R. *Org. Lett.* **2003**, 5, 105–107.
- 91 BARRETT, A. G. M.; CRAMP, S. M.; ROBERTS, R. S. *Org. Lett.* **1999**, 1, 1083–1086.
- 92 BOLM, C.; DINTER, C. L.; SEGER, A.; HÖCKER, H.; BROZIO, J. *J. Org. Chem.* **1999**, 64, 5730–5731.
- 93 BOLM, C.; TANYELI, C.; GRENZ, A.; DINTER, C. L. *Adv. Synth. Catal.* **2002**, 344, 649–656.
- 94 BUCHMEISER, M. R.; WURST, K. *J. Am. Chem. Soc.* **1999**, 121, 11101–11107.
- 95 BUCHMEISER, M. R. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1837–1840.
- 96 (a) KROLL, R.; ESCHBAUMER, C.; SCHUBERT, U. S.; BUCHMEISER, M. R.; WURST, K. *Macromol. Chem. Phys.* **2001**, 202, 645–653. (b) BUCHMEISER, M. R.; KROLL, R.; WURST, K.; SCHEREINA, T.; KEMPE, R.; ESCHBAUMER, C.; SCHUBERT, U. S. *Macromol. Symp.* **2001**, 164, 187–196.
- 97 (a) SILBER, J.; SCHAREINA, T.; KEMPE, R.; WURST, K.; BUCHMEISER, M. R. *J. Organomet. Chem.* **2001**, 622, 6–18. (b) BUCHMEISER, M. R.; SCHAREINA, T.; KEMPE, R.; WURST, K. *J. Organomet. Chem.* **2001**, 634, 39–46.
- 98 BALL, C. P.; BARRETT, A. G. M.; POITOUT, L. F.; SMITH, M. L.; THORN, Z. E. *Chem. Commun.* **1998**, 2453–2454.
- 99 ENHOLM, E. J.; GALLAGHER, M. E. *Org. Lett.* **2001**, 3, 3397–3399.
- 100 ENHOLM, E. J.; COTTONE, J. S. *Org. Lett.* **2001**, 3, 3959–3962.
- 101 HARNED, A. M.; MUKHERJEE, S.; FLYNN, D. L.; HANSON, P. R. *Org. Lett.* **2003**, 5, 15–18.

2.11

Metal-Catalyzed Olefin Metathesis in Metal Coordination Spheres

Eike B. Bauer and J. A. Gladysz

2.11.1

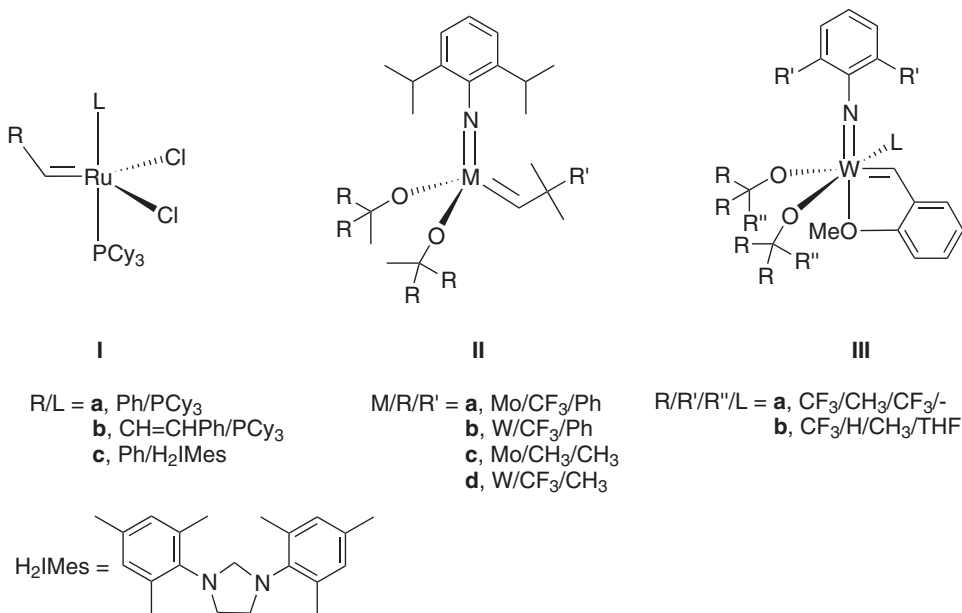
Introduction

The idea of using a transition-metal catalyst to carry out a reaction on a transition-metal-containing substrate might at first seem to be a high-risk proposition. Metal catalysts commonly involve a sequence of reactive, coordinatively unsaturated intermediates. The metal-containing substrate might have labile ligands, Lewis basic sites, or (if cationic) counter-anions that could interact with the coordinatively unsaturated active catalyst. The metal-containing substrate might itself be coordinatively unsaturated, and scavenge ligands that dissociate from the catalyst. In short, there is abundant opportunity for chemical chaos and a failed synthesis.

However, synthetic chemists are seldom deterred by what is seemingly impossible. As illustrated by the other contributions in this monograph, modern olefin metathesis catalysts can be applied to an incredibly wide range of substrates. If used as the focal point of a grant application a decade ago, many of these transformations would have been the basis for a rejection. Thus, despite the potential problems noted above, olefin metathesis has in fact proved possible with numerous transition-metal-containing substrates. This chapter provides a current overview of this rapidly growing subject.

Interest in such reactions arises from a variety of standpoints. For example, ROMP reactions of metal-containing substrates lead to metal-containing polymers. Accordingly, olefin metathesis provides numerous opportunities for preparing new types of organometallic and inorganic materials. Organometallic and coordination compounds are also rapidly coming of age as synthetic building blocks [1, 2], and olefin metathesis provides a unique way of efficiently accessing certain structural units. In a similar vein, synthetic efforts directed at complex organometallic or inorganic target molecules are rapidly increasing. In pursuit of these objectives, many types of reactions not traditionally applied in metal coordination spheres are being investigated. Metals are also potential protecting groups for functionality that might react with olefin metathesis catalysts.

Due to page limitations, it is not possible to treat every example of the title reaction in detail. However, all classes of applications are represented in the graphics.



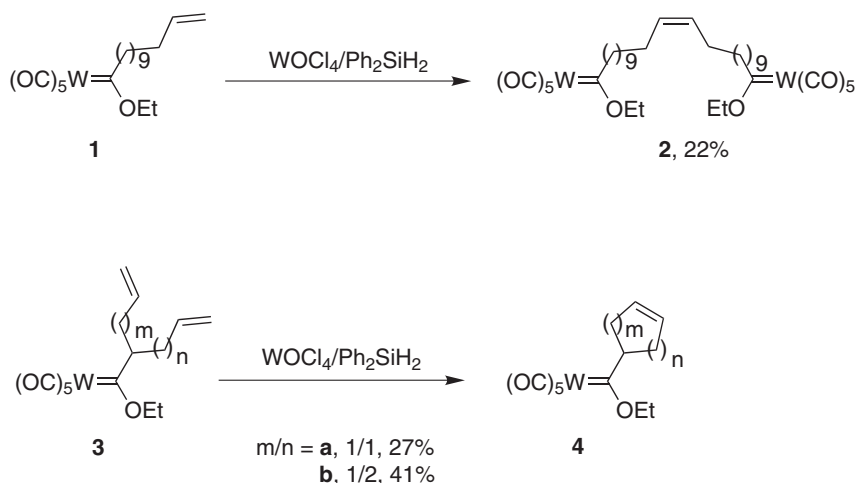
Scheme 2.11-1

To the authors' knowledge, the reference list is comprehensive. Stoichiometric metatheses – such as the reaction of a carbene or alkylidene complex with an olefin to give a new carbene or alkylidene complex and a new olefin – are excluded. Data are presented from a roughly chronological perspective. The most common families of catalysts, the Grubbs-type ruthenium alkylidene complexes and Schrock-type molybdenum or tungsten alkylidene complexes, are abbreviated **I–III** as summarized in Scheme 2.11-1. Reaction conditions are not detailed, but some heating is usually employed and catalyst loadings are commonly in the 2–8 mol% range.

2.11.2

Earliest Literature

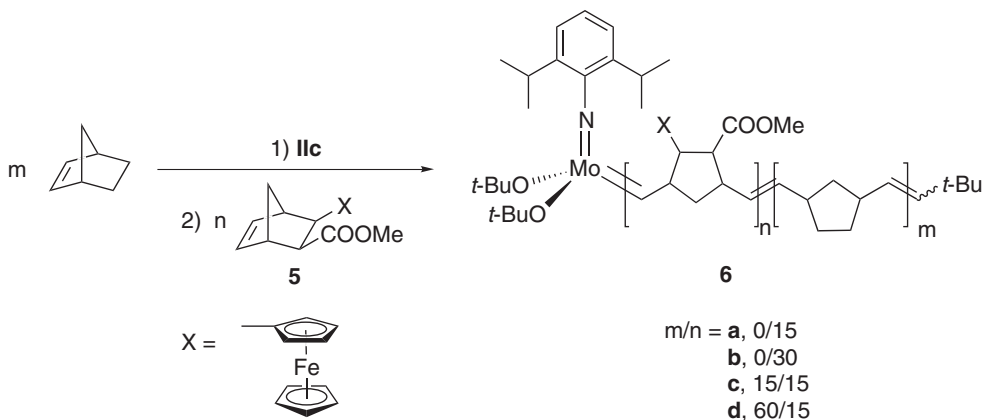
To the best of the authors' knowledge, the first examples of olefin metatheses in metal coordination spheres were reported by Rudler [3, 4]. He investigated the tungsten Fischer carbene complexes **1** and **3a,b** shown in Scheme 2.11-2. Application of a WOCl₄/Ph₂SiH₂ catalyst gave the intermolecularly coupled product **2** and the intramolecularly cyclized products **4a** and **4b**. Although turnover numbers were low (<4), it is nonetheless impressive that the coordinated =C(OEt)R moieties in **1** and **3a,b** did not react or inhibit the reaction.



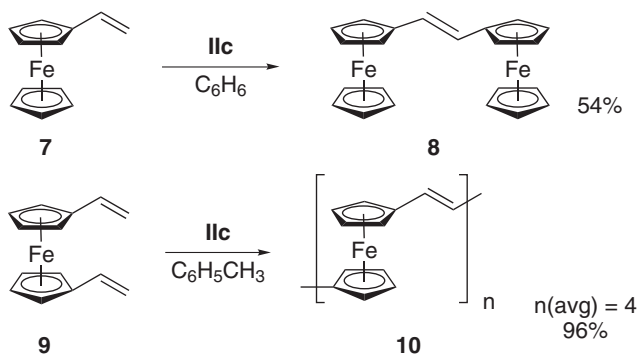
Scheme 2.11-2

2.11.3 Ferrocenes

Ferrocene is one of the most robust platforms for synthetic organometallic chemistry. It is therefore no surprise that metatheses of ferrocene-containing olefins were evaluated early and found to be successful. Scheme 2.11-3 shows the first examples, which were reported by Schrock and Wrighton [5]. Depending upon conditions, norbornene and the ferrocene-substituted norbornene **5** could be elaborated to either living homopolymers (**6a,b**) or block copolymers (**6c,d**). Shortly thereafter, Boncella reported the conversion of the vinyl ferrocenes **7** and **9** in Scheme 2.11-4 to the diferrocene **8** and the conjugated oligomer **10** [6]. The insol-

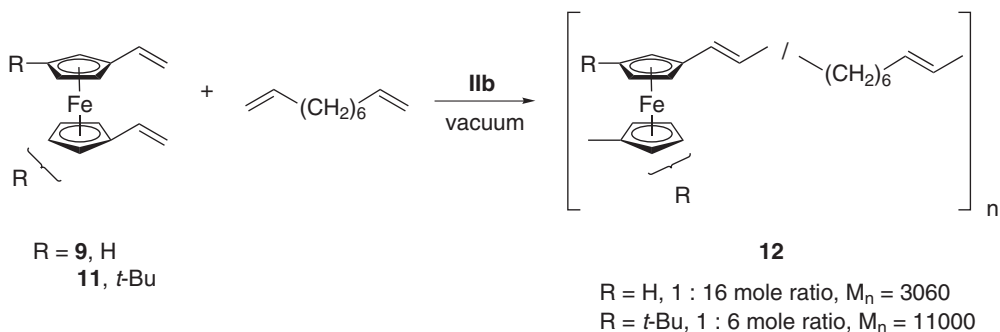


Scheme 2.11-3

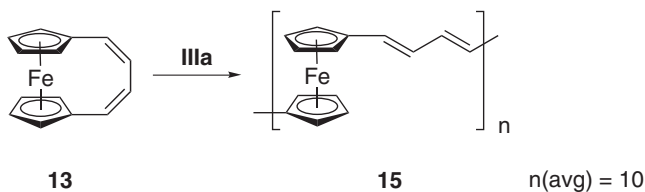


Scheme 2.11-4

ubility of **10** presented problems, but the much more soluble random copolymer **12** could be prepared (Scheme 2.11-5). In contrast to **6c,d**, **10** and **12** feature ferrocene moieties in the polymer backbones.

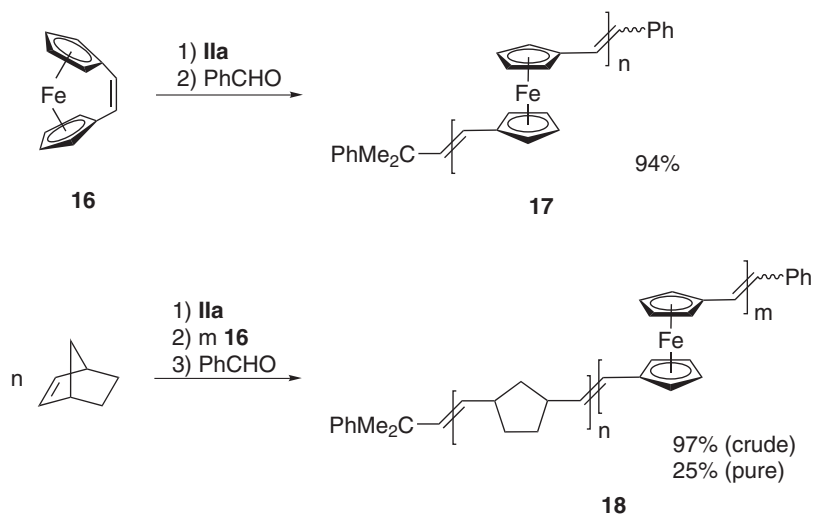


Scheme 2.11-5



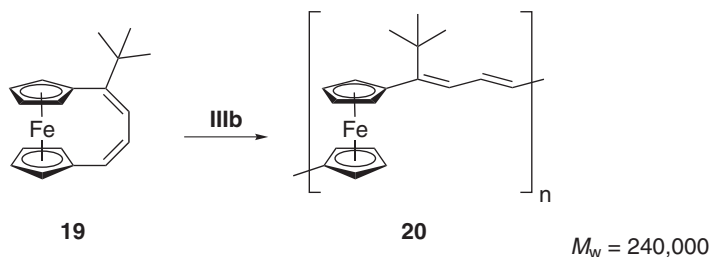
Scheme 2.11-6

Grubbs and Lewis used the unsaturated [4]ferrocenophane **13** shown in Scheme 2.11-6 to prepare the conjugated homopolymer **15** [7]. Tilley subsequently reported that the strained [2]ferrocenophane **16** in Scheme 2.11-7 could be used to synthesize the homopolymer **17** (comparable to **10** in Scheme 2.11-4) and the block copolymer **18** [8]. Like **10**, **15** and **17** were poorly soluble. However, Lee found that the *t*-butyl substituted [4]ferrocenophane **19** shown in Scheme 2.11-8 gave the nicely soluble homopolymer **20** [9]. Nguyen and Mirkin have used other types of



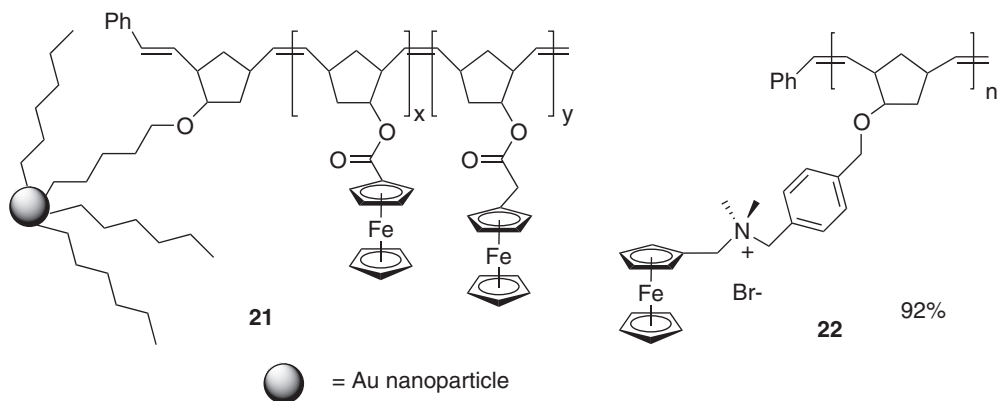
Scheme 2.11-7

monomers to synthesize gold nanoparticles with block copolymer shell structures, as illustrated by **21** in Scheme 2.11-9 [10]. They have also reported amphiphilic polymers of the type **22** [11]. Redox and/or conductivity properties of the Schrock/Wrighton, Grubbs/Lewis, Tilley, and Nguyen/Mirkin polymers have been investigated.



Scheme 2.11-8

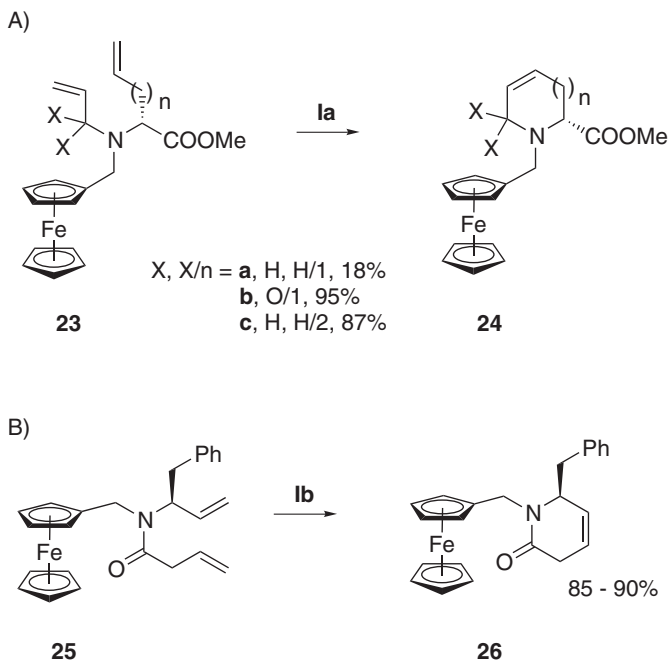
Olefin metathesis has also been used to synthesize various monoferrocene species. For example, Rutjes and Guibé have reported the ring-closing metatheses in Scheme 2.11-10 [12, 13]. In both studies, the ferrocene is part of a protecting group for the amide nitrogen. Richards, Ogasawara, and Hayashi have described the transannular ring-closing metatheses of 1,1'-diallylferrocenes depicted in Scheme 2.11-11 [14, 15]. Richards was the first to report the conversion of the parent compound **27** to the [4]ferrocenophane **28** (Scheme 2.11-11A), using Grubbs' catalyst **Ia** at 130 °C. He also reacted mixtures of the *meso* and *rac* diastereomers of **29a–c** under similar conditions. For clarity, these are presented as separate equations (Schemes 2.11-11B and 2.11-11C). In all cases, the *meso* diastereomers readily



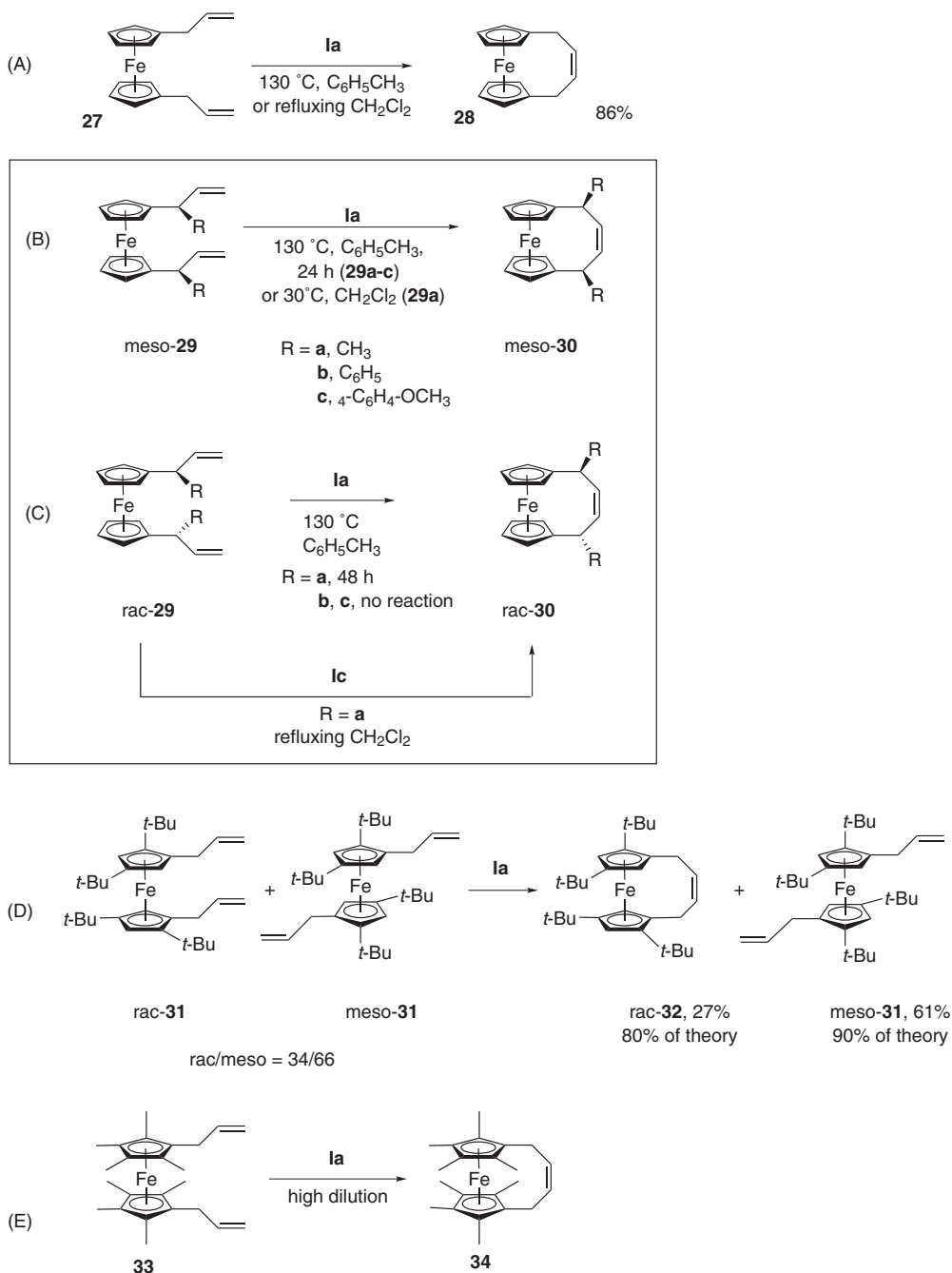
Scheme 2.11-9

cyclized to give *meso*-**30a–c**. However, only *rac*-**29a** underwent metathesis, and significantly longer reaction times were required.

Similar reactions of **27** and **29a** in warm CH_2Cl_2 were later reported by Ogasawara and Hayashi. Under their milder conditions, *rac*-**29a** did not react at all. However, the newer-generation catalyst **Ic** effected ring-closing metathesis. Ogasawara and Hayashi found a similarly high diastereoselectivity with the diallylfer-



Scheme 2.11-10



Scheme 2.11-11

rocene **31** (Scheme 2.11-11D), which features two planar chirality elements. Here the *rac* isomer underwent reaction, and the *meso* diastereomer was recovered unchanged. Transannular interactions between the *t*-butyl groups are probably greater for the *meso* cyclization. Ogasawara and Hayashi also investigated additional achiral systems, such as the $\text{CH}_2\text{CH}=\text{CHCH}_3$ analogue of **27** (slower but high-yield cyclization) and the ruthenium analogue of **27** (92% under higher dilution conditions). For the octamethyl substrate **33** (Scheme 2.11-11E), high dilution conditions were absolutely necessary to avoid polymer formation.

Lovely and Kawai have developed the cross-metatheses illustrated in Scheme 2.11-12 [16–18]. The vinyl ferrocene **7** can be used to prepare molecules with extended π conjugation. Only small amounts of homodimers form.

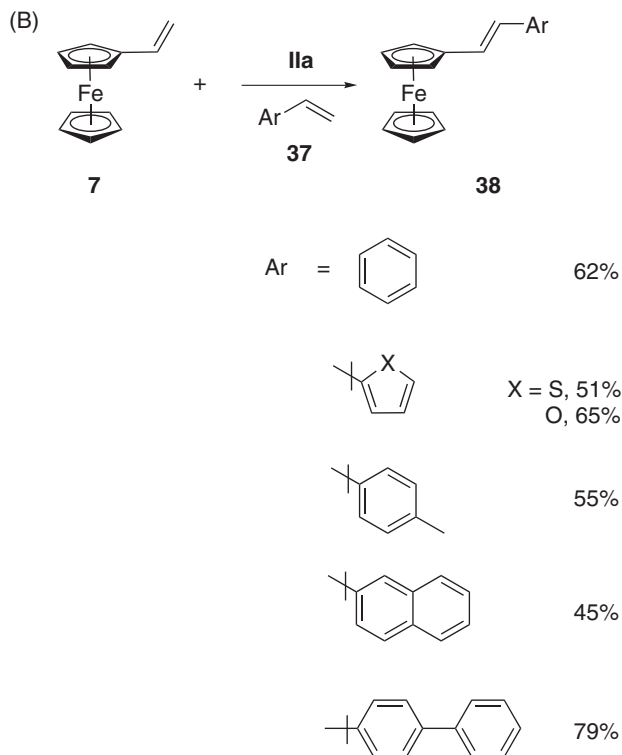
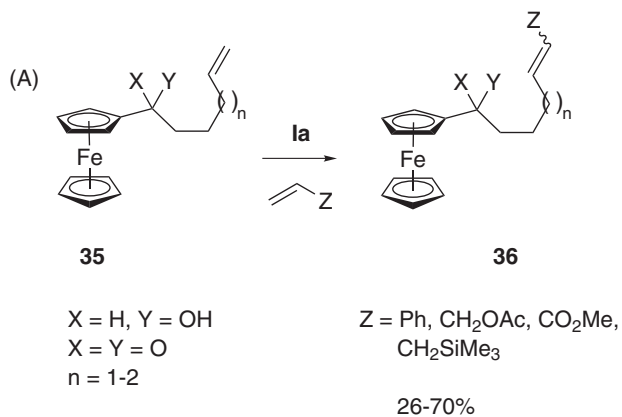
2.11.4

Sophisticated Target Molecules: Catenanes and Knots

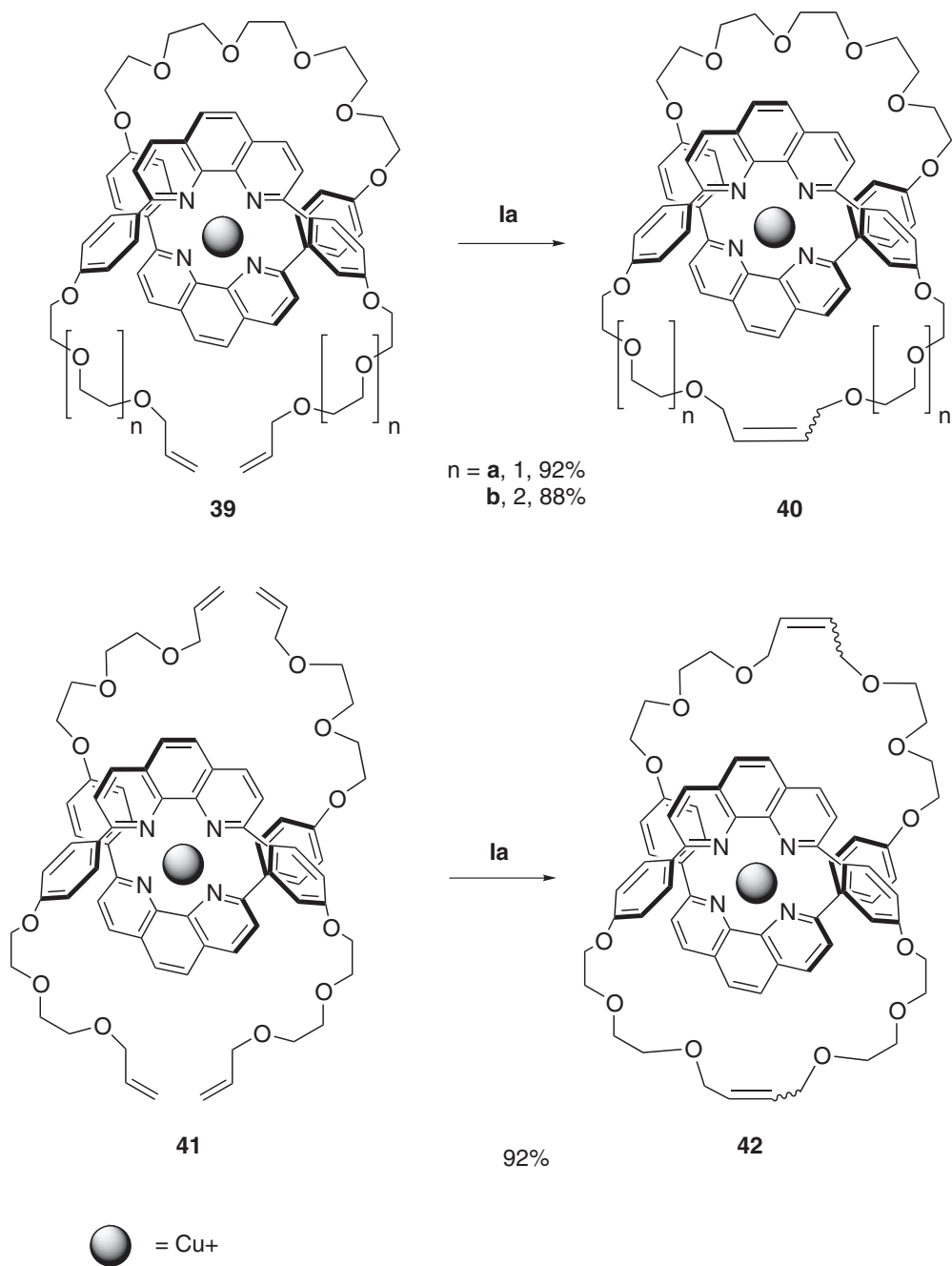
Shortly after metatheses of ferrocene-containing olefins began to appear, Sauvage described breathtaking applications in the area of catenane synthesis [19–24]. Sauvage's strategy was to use a metal to template two polydentate ligands in "orthogonal" coordination geometries. Appropriately positioned flexible substituents of sufficient lengths would then be able to adopt conformations that nearly encircle the orthogonal ligand. Following a twofold macrocyclization, the metal would be removed, leaving two interlocked rings behind. Sauvage had investigated a number of macrocyclization protocols [25]. However, olefin metathesis proved distinctly superior. His first data were obtained with Grubbs and involved the copper complexes **39** and **41** in Scheme 2.11-13 [19, 20]. The products **40a**, **40b**, and **42**, which contain interlocked 32-, 38-, and 32-membered rings, were obtained in high yields. Importantly, it was further possible to hydrogenate the C=C residues in high yields.

Sauvage then investigated substrates in which two metals are linked by (bis)-polydentate diolefinic ligands, as exemplified by the copper and iron complexes **43** and **45** in Scheme 2.11-14 [21, 23]. As compared to **39** and **41**, these feature an extra "crossing" of the diolefin moieties. Accordingly, metatheses afford trefoil knots with 82- and 112-membered rings (**44**, **46**). Related substrates with three "crossings" were investigated and led to doubly interlocked catenanes such as the copper complex **47** (Scheme 2.11-14) [22]. However, in this sequence olefin metathesis was actually conducted with a lithium complex, and the copper was introduced later.

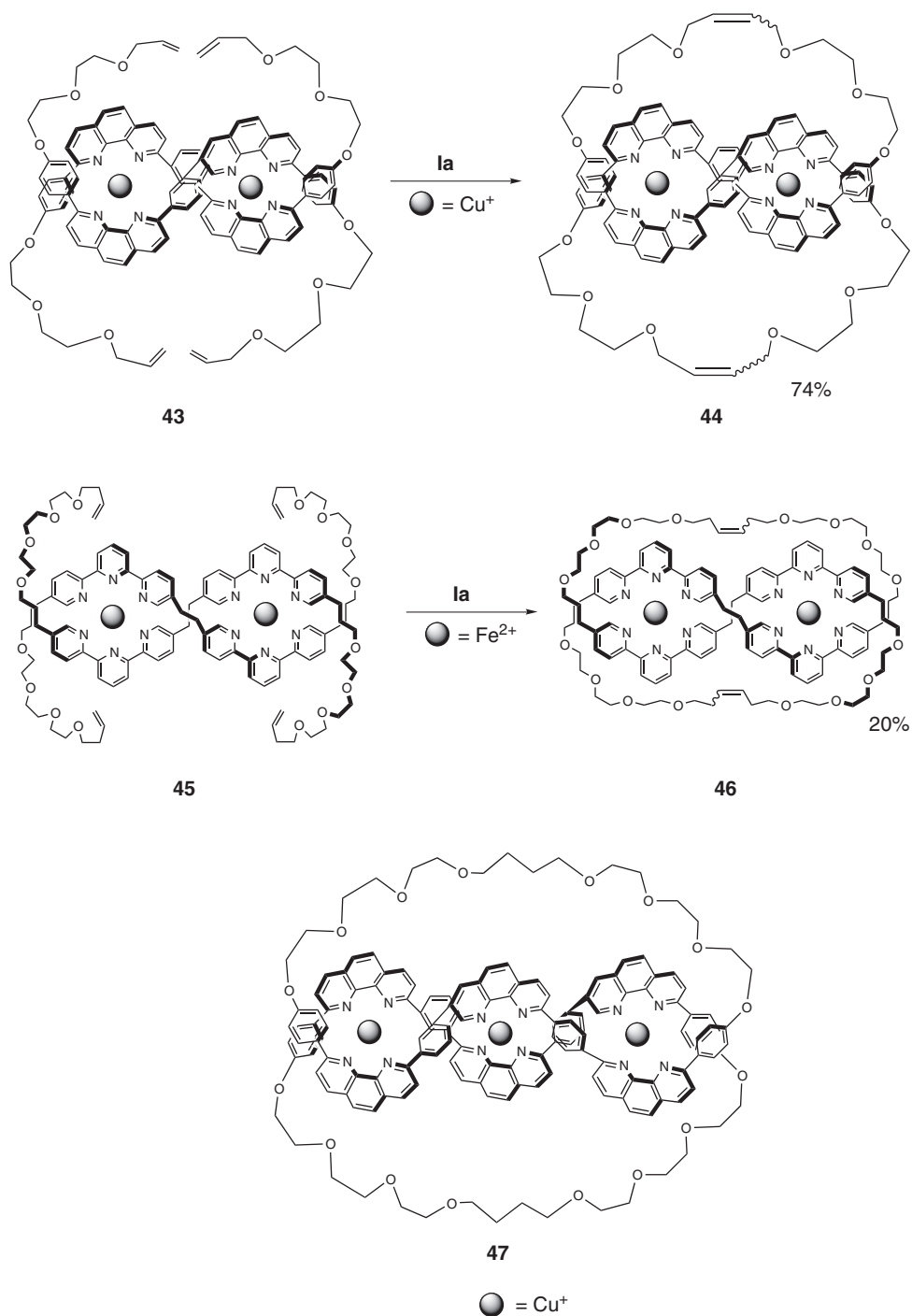
The metathesis of the iron complex **48** in Scheme 2.11-15 affords the 58-membered monomacrocycle **49** as opposed to a catenane [24]. This illustrates that the exact type of product obtained is a sensitive function of the ligand and metal. Nonetheless, Sauvage's many successes, encompassing several different metals and charge states, clearly suggested to the authors that olefin metathesis might be generally applicable in metal coordination spheres.



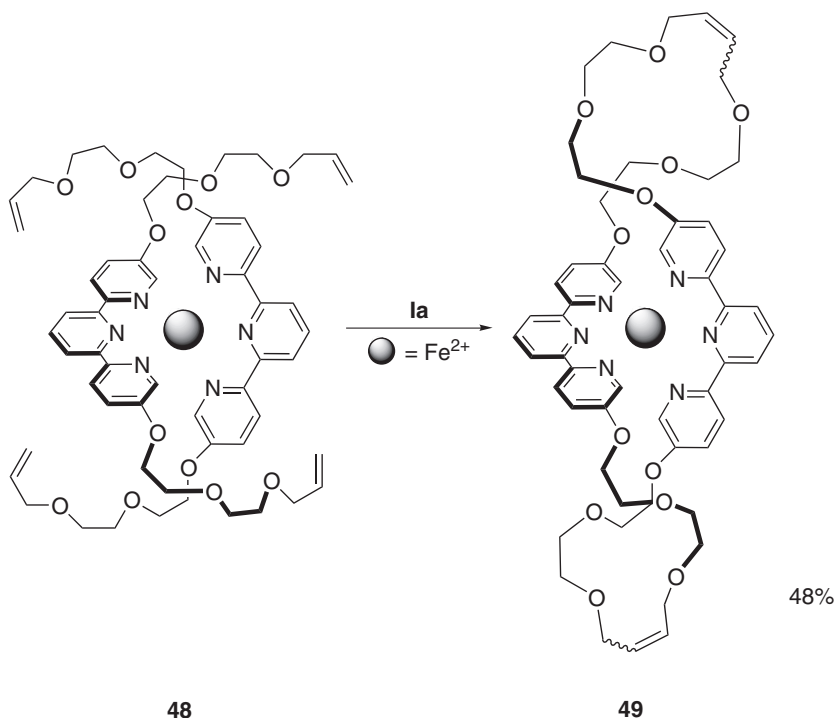
Scheme 2.11-12



Scheme 2.11-13



Scheme 2.11-14



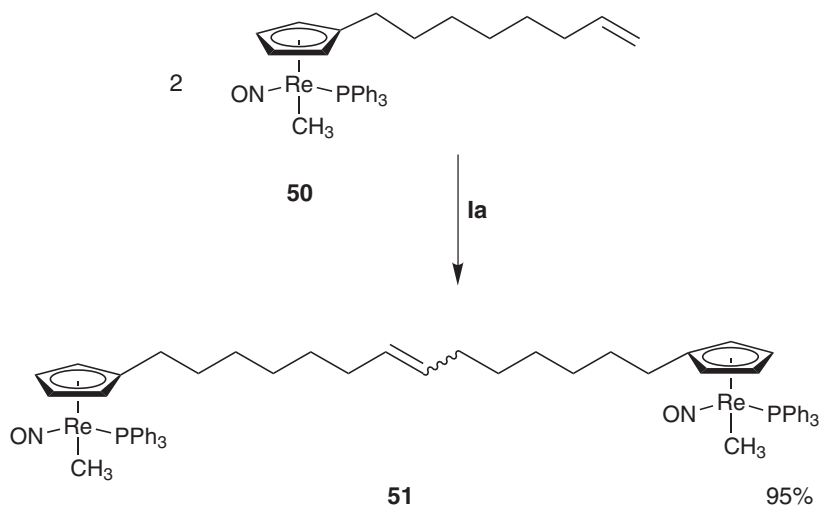
Scheme 2.11-15

2.11.5

Systematic Investigation of Reaction Scope

With the above chemistry as inspiration, the authors' team set out to systematically study the effect of coordination geometry, valence electron count, and charge of the substrate on olefin metathesis [26–32]. These efforts were designed to address several distinct types of cyclization modes: cyclization within a ligand, cyclization between *cis* ligands, cyclization between *trans* ligands, and topologically more complex polycyclizations. The reaction of **50** shown in Scheme 2.11-16 was also conducted to make sure that intermolecular metathesis would not be problematic [28]. Note that the chiral rhenium fragment has 18 valence electrons.

Olefin metatheses that involve cyclization within a diolefinic ligand are presented in Scheme 2.11-17 [26, 28]. Substrates **52** and **54** show that small ring heterocycles can be efficiently generated. Substrates **56a** and **56b** show that cationic and neutral 15-membered macrocycles can be obtained in similar yields. Interestingly, ultrahigh dilution is not necessary to suppress intermolecular reactions. Phenomena analogous to the gem-dialkyl (Thorpe-Ingold) effect in carbocyclizations are believed to help promote cyclization [28]. Since the chiral rhenium moiety is relatively robust, other metal fragments were investigated next.



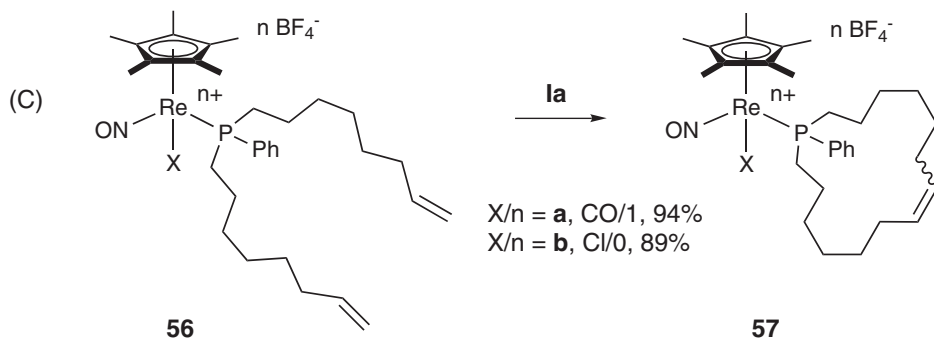
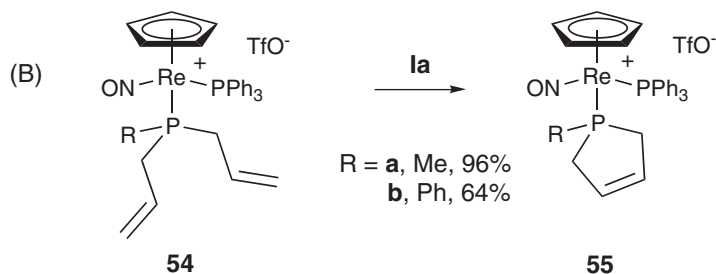
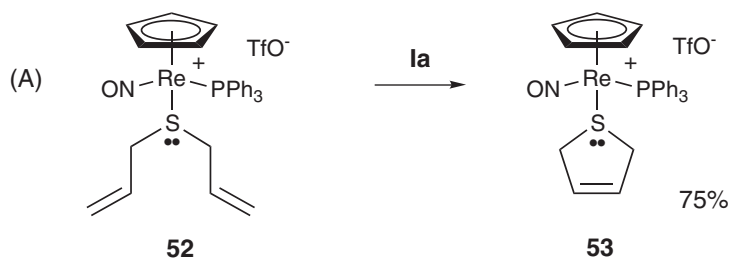
Scheme 2.11-16

Accordingly, the octahedral rhenium complex **58** in Scheme 2.11-18 features six monodentate ligands, two of which are monoolefinic *cis*-phosphines [26, 28]. Metathesis proceeded in high yield to give the 17-membered macrocycle **59**. Here the metal is a part of the ring, as opposed to a ring substituent as in Scheme 2.11-17. Both **59** and **57** (Scheme 2.11-17) could be hydrogenated to saturated macrocycles.

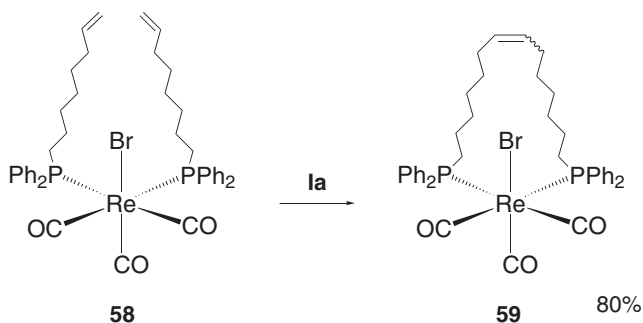
It was next investigated whether coordinatively unsaturated complexes could also be viable substrates. As shown in Scheme 2.11-19, several 16-valence-electron square planar platinum complexes with *cis* monoolefinic phosphine or sulfide ligands (**60**) were investigated [26, 28]. All gave macrocyclizations in good yields. In most cases, minor amounts of dimeric diplatinum products (**62**) were detected. With the diphosphorus ligand, the mono- and diplatinum species appear to be in facile equilibrium. Therefore, either (but most likely the former) could be the dominant kinetic product. With the disulfur ligands, the monoplatinum and diplatinum products are separable and are therefore more likely to represent primary metathesis products.

Attention was then turned to more challenging types of macrocyclizations. One obvious question was whether *trans*-spanning ligands might be constructed. As shown in Scheme 2.11-20, the square planar rhodium and platinum complexes **63a** and **63b** were investigated [27, 28]. In both cases, high yields of 17-membered macrocycles were obtained. In the platinum series, analogous 13-, 21-, and 25-membered macrocycles have been similarly prepared [31]. However, no convincing steric or electronic driving force for intramolecular as opposed to intermolecular metathesis has yet been identified. The C=C linkages in all of these systems are readily hydrogenated.

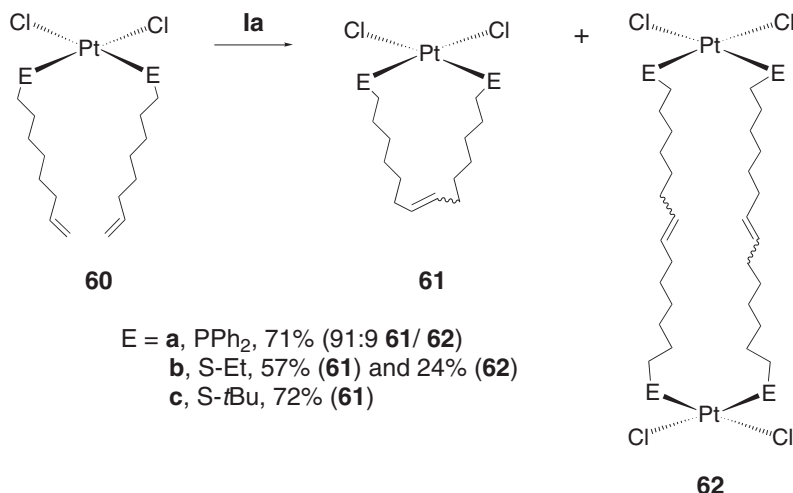
Complexity increases when two or more diolefinic ligands are present. Ring



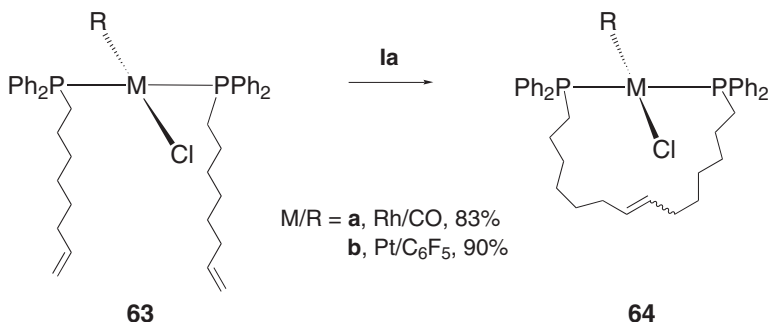
Scheme 2.11-17



Scheme 2.11-18



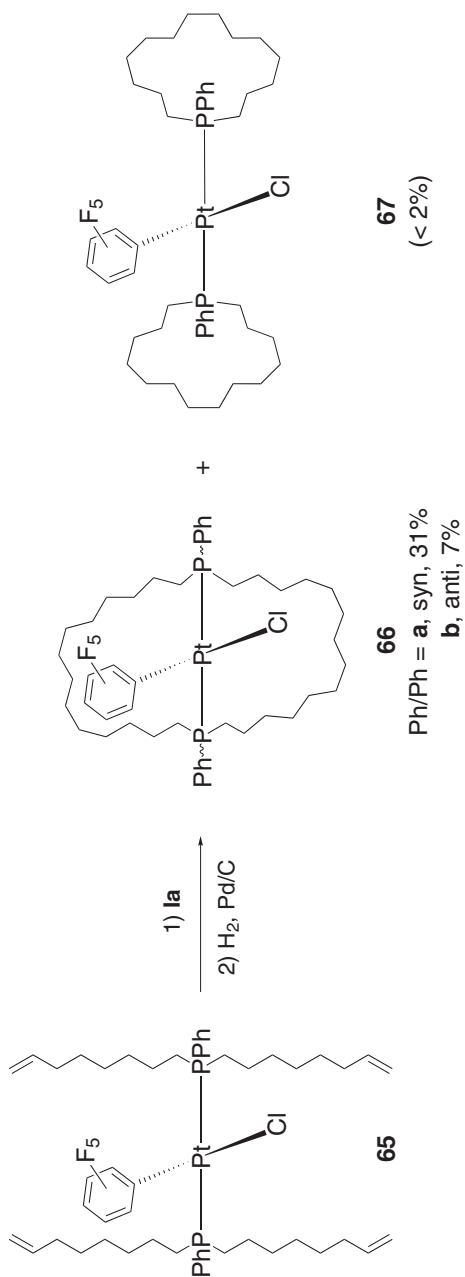
Scheme 2.11-19



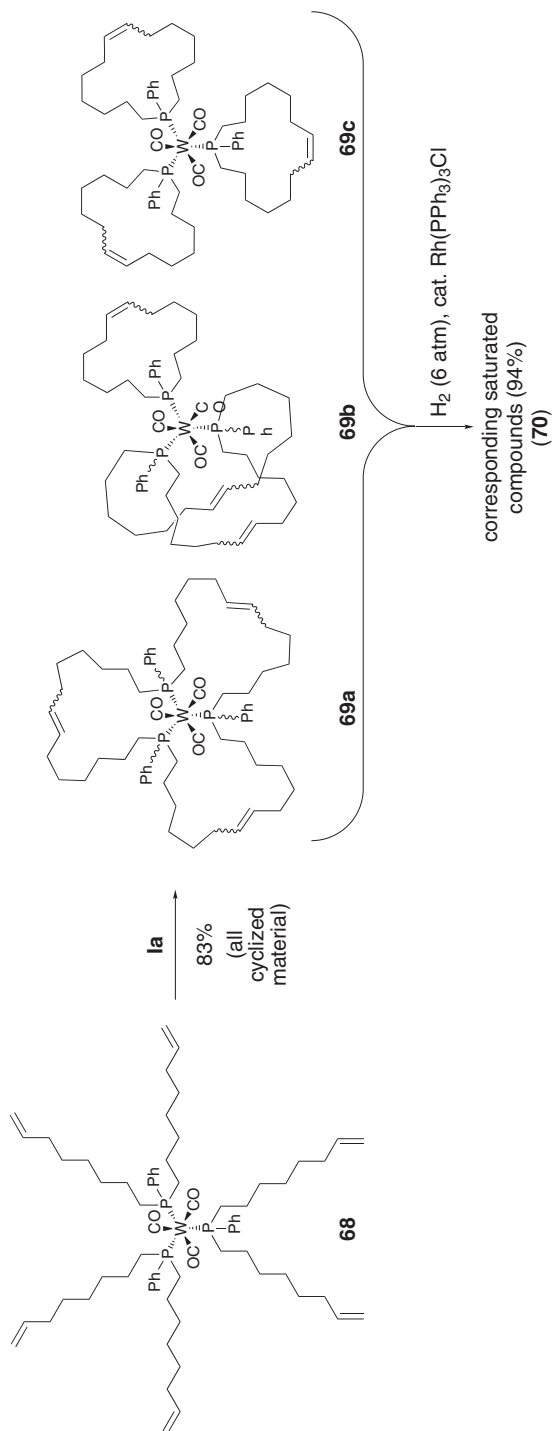
Scheme 2.11-20

closing can take place within or between the ligands. Scheme 2.11-21 shows a platinum complex **65** with two *trans* diolefinic phosphines – identical to that in **56a,b** (Scheme 2.11-17). Surprisingly, macrocyclization preferentially occurs between ligands to give doubly *trans*-spanning diphosphine complexes [27]. To simplify analysis, products were characterized after hydrogenation. Two isomers of **66**, differing in the relative orientations of the phenyl groups on phosphorus, were isolated in 38% combined yield. An authentic sample of the alternative product **67** was independently synthesized [31]. Only ca. 2% could be detected by NMR in the crude reaction mixture. Other metathesis products form and are believed to be diplatinum or oligoplatinum species.

As shown in Scheme 2.11-22, the tungsten complex **68**, with three diolefinic phosphines in a facial substitution pattern, has also been investigated [27, 28]. A complex mixture of all three possible types of macrocyclization products, **69a–c**, appears to form. Two isomers of the type **69a**, which feature 45-membered macrocyclic triphosphines, were structurally characterized. Although this represents a



Scheme 2.11-21



Scheme 2.11-22

distinct loss in selectivity as compared to Scheme 2.11-21, diolefinic phosphines with other $(\text{CH}_2)_n$ spacer lengths might behave differently. From a different perspective, Scheme 2.11-22 represents an efficient synthesis of a combinatorial library, for which 38 diastereomers are possible.

2.11.6

Additional Literature Examples

During the course of the authors' studies described in the previous section, further examples of olefin metatheses in metal coordination spheres were reported by other research groups. Some syntheses of medium-sized rings by Paley [33], Dötz [34], and Licandro [35] are collected in Scheme 2.11-23. We find the excellent yields with the highly functionalized 1,3-diene iron tri(carbonyl) complexes **71a–c** (Scheme 2.11-23A) particularly noteworthy. Metatheses of Fischer carbene complexes such as **73**, **75**, **77**, and **79** clearly present no intrinsic difficulty. However, **75a** (Scheme 2.11-23C) underwent decarbonylation to give a carbene/olefin chelate (8%), and the carbon monoxide released is believed to poison the catalyst [34]. Some monoolefin analogues of **77** and **79** (Schemes 2.11-23D,E) undergo intermolecular metathesis, but others do not [35].

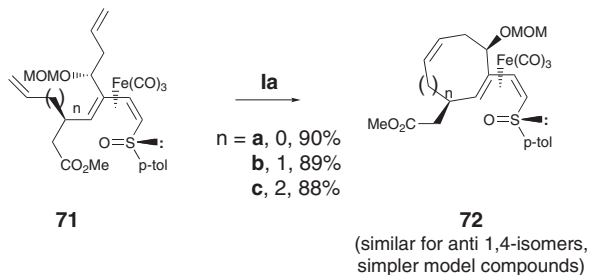
More recently, Green [36] and Young [37] have shown that diolefinic dicobalt hexacarbonyl alkyne complexes are viable substrates for ring-closing metathesis. As illustrated in Scheme 2.11-24, many products with 7-membered rings (**82**, **86**) have been prepared. Eight-membered rings can also be accessed (**84**), but all efforts to generate 6-membered rings have been unsuccessful [36]. Without the cobalt-protecting group, ring-closing metathesis would not be possible because of high product strain, and ene/yne metathesis could also occur.

As depicted in Scheme 2.11-25, Sarkar has described olefin metatheses in the coordination spheres of a variety of arene chromium tricarbonyl complexes [38]. High yields of **88**, **90**, **92**, and **94** were obtained, further extending the already broad synthetic utility of this template in organic synthesis.

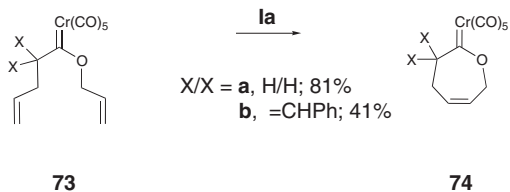
Lambert has studied the metathesis of the *trans* bis(pyridine) complex **96** shown in Scheme 2.11-26 [39]. Each pyridine ligand contains two *ortho* homoallyl groups. Because palladium-nitrogen conformations in which these extend above and below the metal square plane are preferred, there is a strong geometric predisposition towards cyclization between the ligands. Accordingly, the doubly *trans*-spanning macrocycle **97** is isolated in high yield. Analogous driving forces are not present in the examples in Scheme 2.11-21.

van Koten has reported metatheses of diolefinic pyridine ligands in the coordination spheres of pincer complexes [40]. Some representative examples are given in Scheme 2.11-27A. Note that in two of the three cases (**98a**, **101**), considerable olefin isomerization also occurs. With other substrates that lead to more strained metathesis products, isomerization dominates. Recently, Weck has described the ring-opening polymerization of the norbornene-tethered pincer complex **104** shown in Scheme 2.11-27B [41].

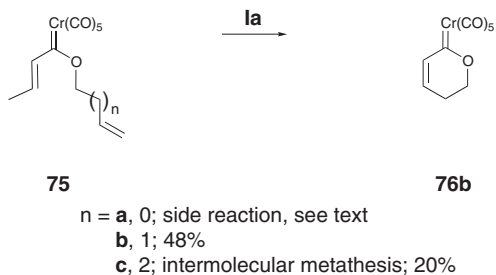
(A)



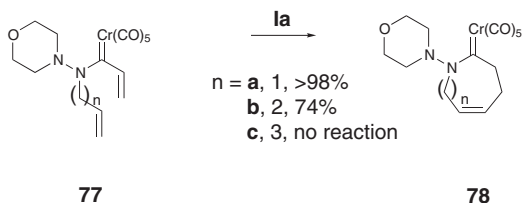
(B)



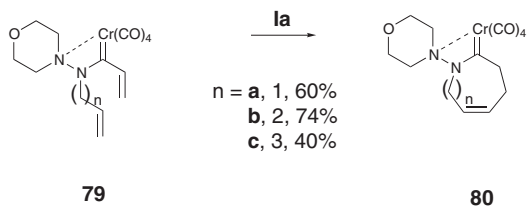
(C)



(D)

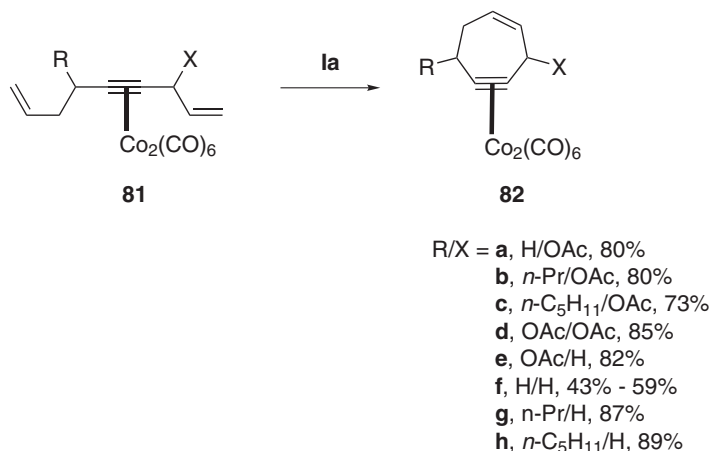


(E)

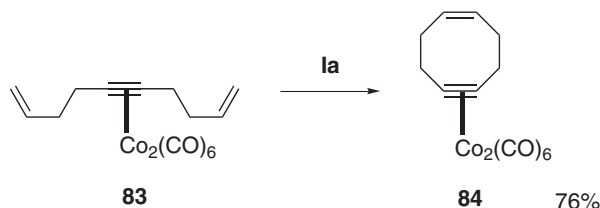


Scheme 2.11-23

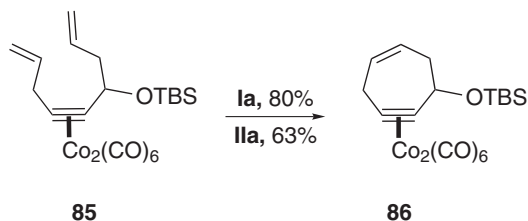
(A)



(B)

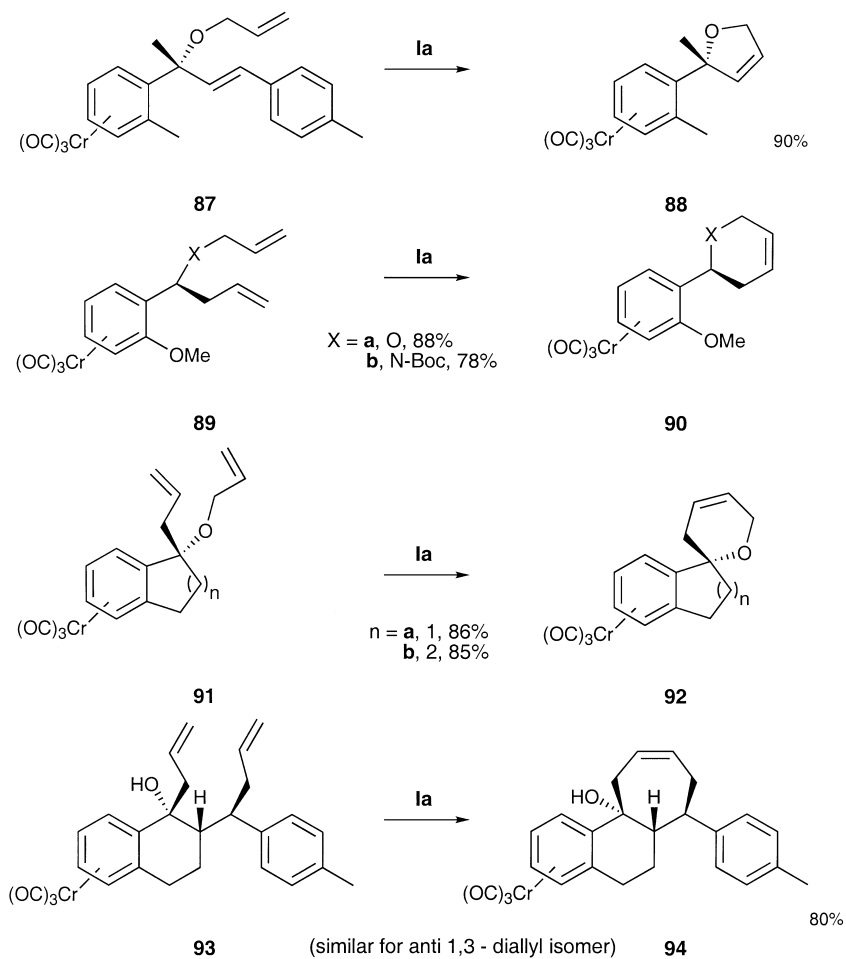


(C)

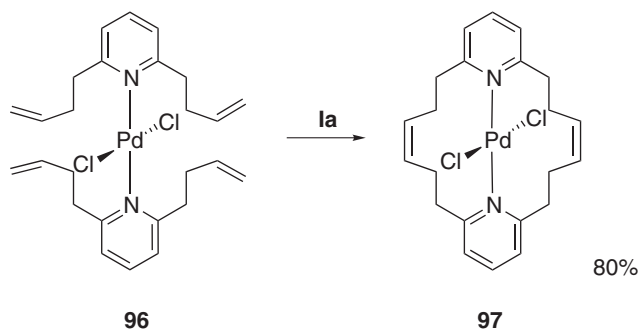


Scheme 2.11-24

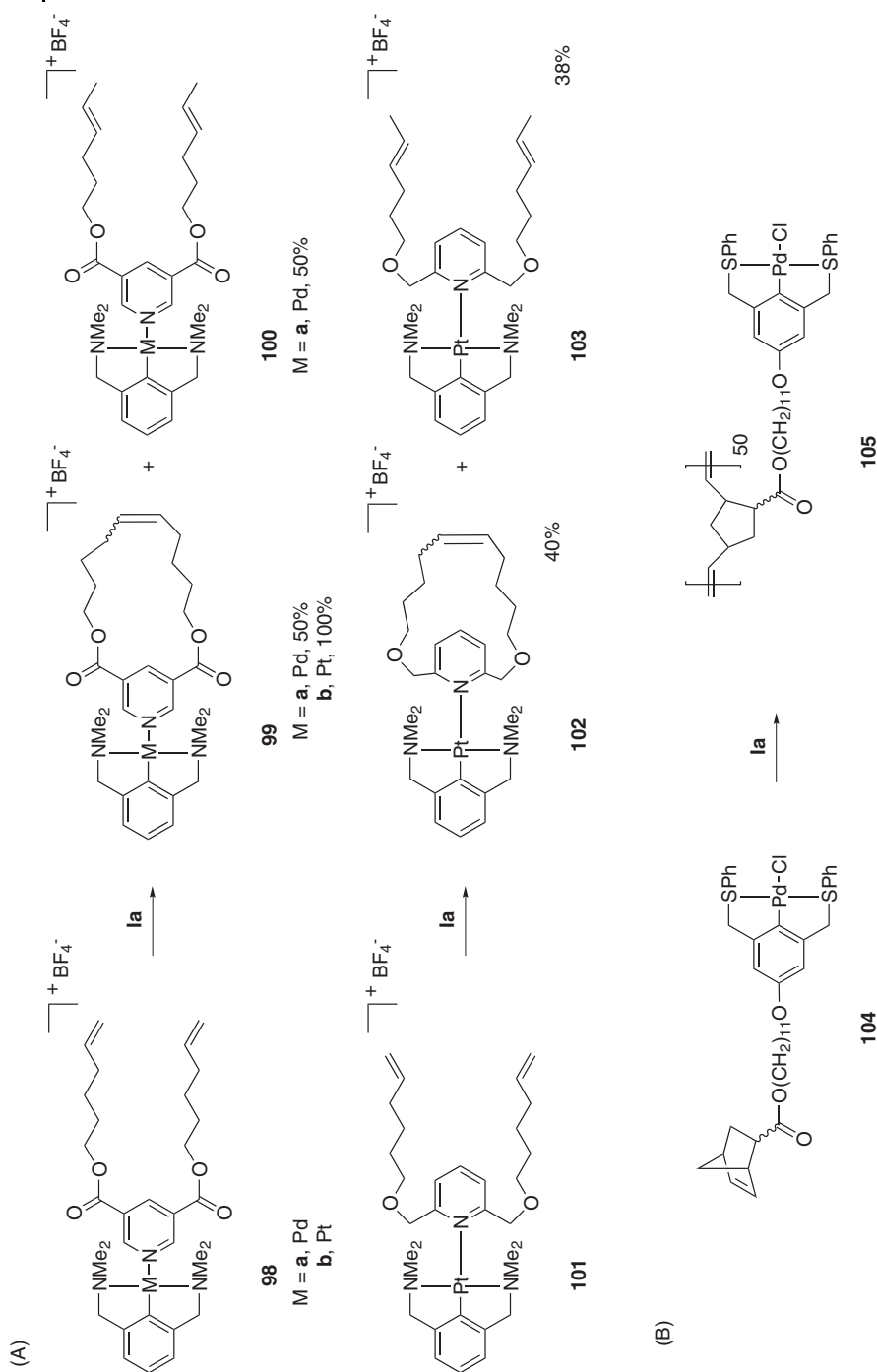
As illustrated in Scheme 2.11-28A, Ogasawara and Hayashi have reported that the group IV diallyl metallocene dichlorides **106a** and **106b** undergo efficient transannular ring-closing metathesis [15]. Similar data with **106a** and **106c** were simultaneously reported by Erker [42]. Ogasawara and Hayashi also prepared a mixture of *meso* and *rac* diastereomers of the zirconocene dichloride **108**. In contrast to the result with the related ferrocene **31** in Scheme 2.11-11, the *meso* diastereomer of **108** gave much faster metathesis with catalyst **Ia**. The *rac* diastereomer could be cyclized with the more reactive catalyst **Ic**. These data have exciting



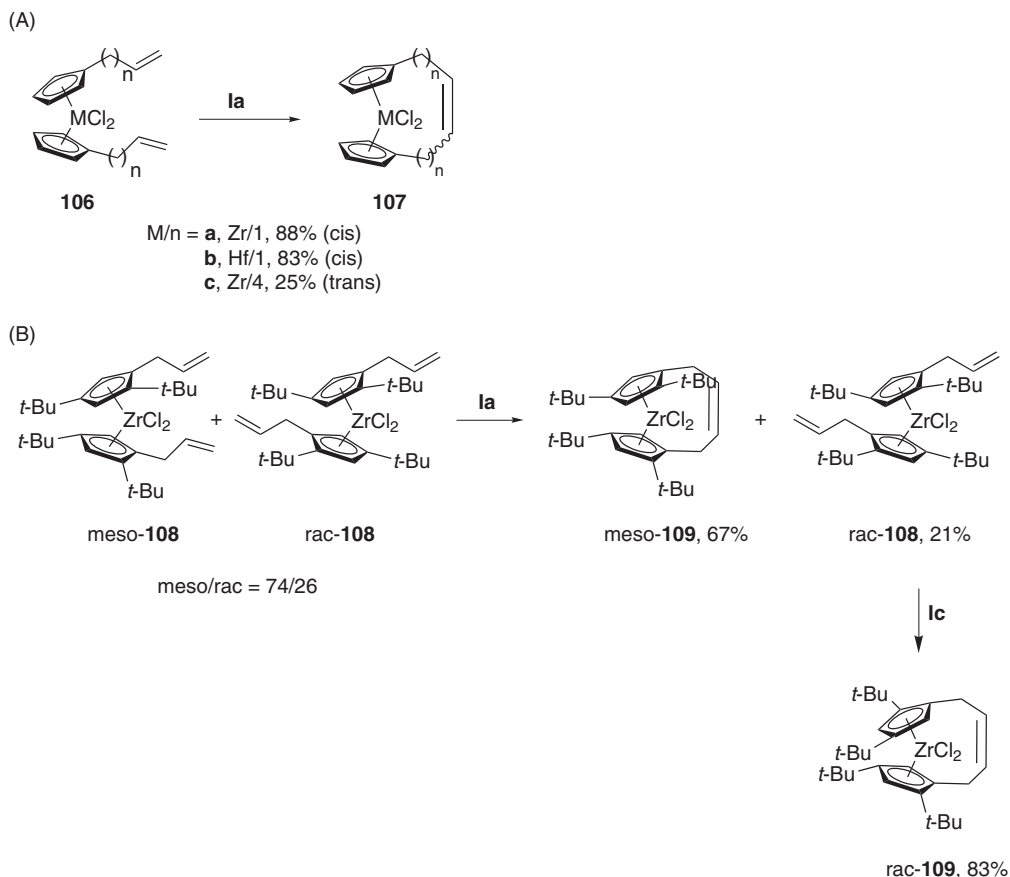
Scheme 2.11-25



Scheme 2.11-26



Scheme 2.11-27



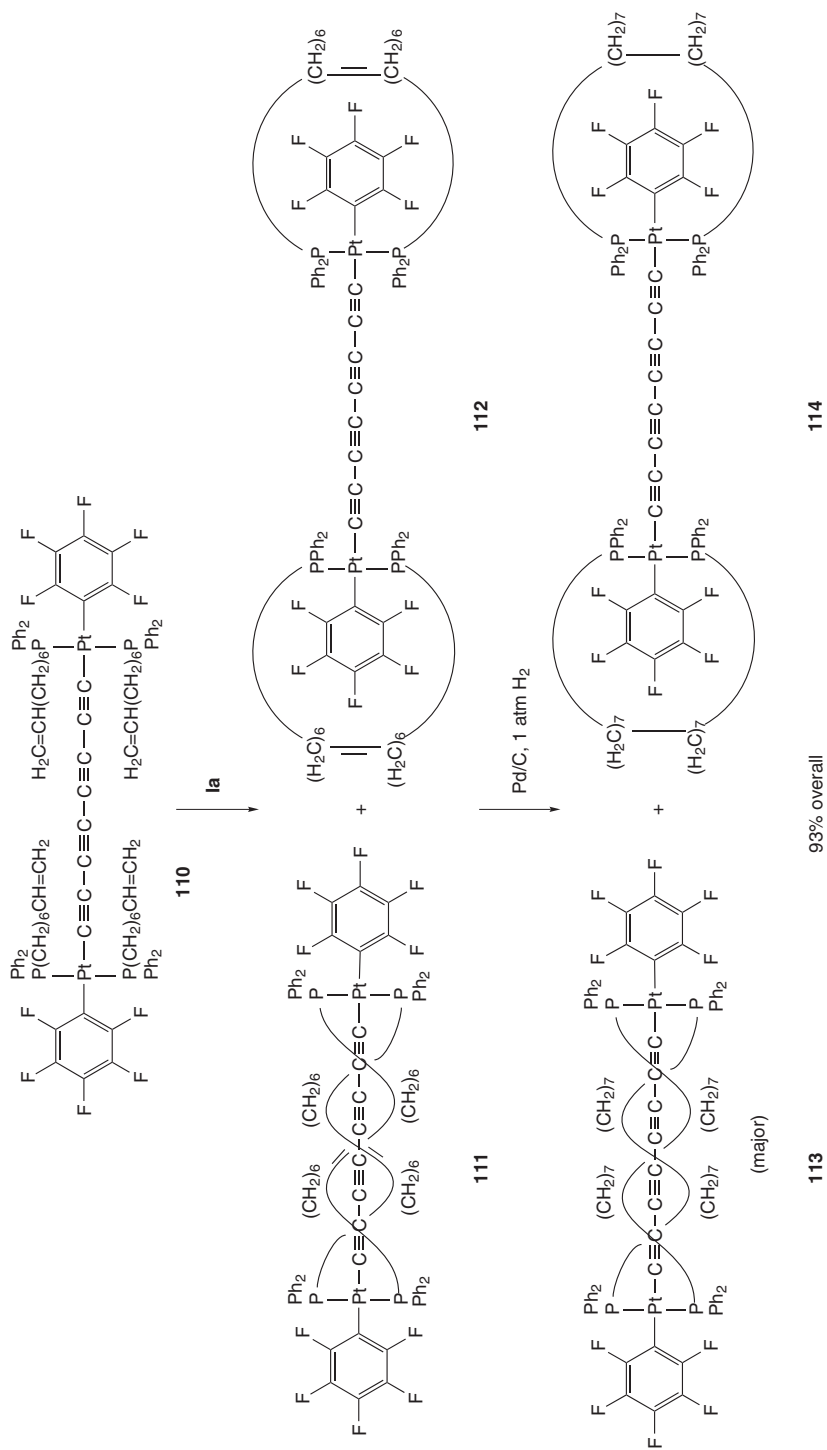
Scheme 2.11-28

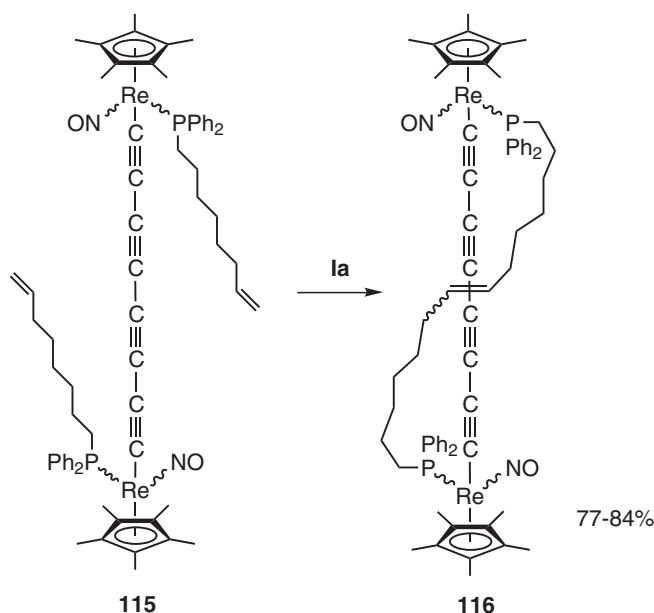
implications for the syntheses of *ansa*-metallocene catalysts for stereoregular olefin polymerization.

2.11.7

Towards Additional Types of Sophisticated Target Molecules

Many of the reactions in Section 2.11.5 were designed to provide precedent for speculative routes to various target molecules under investigation in the authors' laboratory. That of greatest interest is shown in Scheme 2.11-29 [28]. The $\text{PtC}\equiv\text{CC}\equiv\text{CC}\equiv\text{CC}\equiv\text{CPt}$ compound **110** features two *trans* monoolefinic phosphine ligands on each platinum. Metathesis can in theory deliver two types of dimacrocyclic products. One, **111**, arises from cyclization between phosphines on opposite platinum atoms. The other, **112**, arises from cyclization between phosphines on the same platinum atom. Since olefin metathesis catalysts are well known to add to





Scheme 2.11-30

$\text{C}=\text{C}$ linkages [43], many other types of products are also possible. However, **111** and **112** are obtained in high yield, with the former dominating.

In another unexpectedly selective reaction, the hydrogenation of **111** and **112** over Pd/C reduces the $\text{C}=\text{C}$ linkages, but not the $\text{C}\equiv\text{C}$ linkages. Complexes **113** and **114** are isolated after chromatography, and independent syntheses of each have been developed. The former exhibits a fascinating double-helix structure in the solid state, in which the flexible sp^3 carbon chains spiral around the sp carbon chain. The total twist defined by the end groups is 193° ($\text{P}_a\text{-Pt}_a\text{-P}_a\text{-Pt}_b$ vs. $\text{P}_b\text{-Pt}_b\text{-P}_b\text{-Pt}_a$ planes). Analogous sequences have been carried out with different olefinic phosphines and $\text{Pt}(\text{C}\equiv\text{C})_n\text{Pt}$ sp carbon chain lengths [29, 31]. A similar macrocyclization could be effected with the dirhenium compound **115** shown in Scheme 2.11-30 [30]. However, the product **116** represents one of the few cases where $\text{C}=\text{C}$ hydrogenation could not be reproducibly effected without decomposition.

Other types of sophisticated target structures have been pursued by Dijkstra and van Koten [40, 44]. First, the dendrimer-like hexakis (pincer) complex **117** shown in Scheme 2.11-31 was assembled. This contains structural units similar to those of **98** and **101** in Scheme 2.11-27A. A compound derived from macrocyclization between different pyridine ligands was sought (**118**). However, the major meta-thesis product was derived from macrocyclization within pyridine ligands (**119**). Disappointingly, the olefin isomerization product **120** dominated. Nonetheless, **118** and **119** represent types of molecules that may become accessible in high yields as new-generation olefin metathesis catalysts are developed.



Scheme 2.11-31

2.11.8

Summary

The preceding examples indicate few if any restrictions on the types of metal-containing olefins that can be applied in olefin metathesis reactions. Both Grubbs- and Schrock-type catalysts (I–III) can be utilized for the construction of numerous classes of acyclic, cyclic, and macrocyclic compounds from readily accessed precursors. There are very few reports of failures or side reactions other than those mentioned in passing above [45]. In many cases, problems could be solved with newer-generation ruthenium catalysts. Although mixtures of C=C isomers are produced, these can almost always be hydrogenated in high yield. Furthermore, reports of C≡C metatheses in metal coordination spheres – which by definition cannot yield geometric isomers – are now beginning to appear [46, 47].

Surprisingly, macrocycles are often obtained in high yields without resorting to ultrahigh dilution. Very high selectivities with respect to inter/intra-ligand cyclizations and *meso/rac* substrates can also be observed. The field is obviously ripe for extensions to enantioselective catalysts [48], such as kinetic resolutions of the enantiomers of *rac* diastereomers. In conclusion, the stage is firmly set for the widespread deployment and systematic application of olefin metathesis in targeted syntheses of complex and/or topologically novel inorganic and organometallic systems.

2.11.9

Addendum

Since the submission of this manuscript in late 2002, the following additional papers have been published or brought to the authors' attention. First, block copolymers similar to **6** in Scheme 2.11-3 with cyclopentadienyl palladium and platinum species in place of the ferrocenyl moiety have been described [49]. Related polymers with zinc/1,4-diamine chelates have also been reported [50]. Additional examples of catenane syntheses (Schemes 2.11-13 and 2.11-14) have appeared [51], and metatheses of Fischer carbene complexes (Scheme 2.11-23) have been extended [52]. Further ring-closing metatheses of cobalt alkyne complexes (Scheme 2.11-24) have been published [53]. Novel ansa-heteroferrocenes related to the systems in Schemes 2.11-11 have been described [54], and dinuclear titanium and zirconium sandwich and half-sandwich complexes synthesized [55]. A macrotricyclization of an analog of **117** (Scheme 2.11-31) with a 1,3,5-trisubstituted benzene core was spectacularly successful [56].

Acknowledgments

The authors thank the DFG (300/1-2) for supporting their research.

References

- 1 TOR, Y. *Synlett* **2002**, 1043.
- 2 GLADYSZ, J. A.; DELACROIX, O. *Chem. Commun.* **2003**, 665 (feature article).
- 3 ALVAREZ TOLEDANO, C.; PARLIER, A.; RUDLER, H.; DARAN, J.-C.; JEANNIN, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 576.
- 4 ALVAREZ, C.; PACREAU, A.; PARLIER, A.; RUDLER, H.; DARAN, J.-C. *Organo-metallics* **1987**, 6, 1057.
- 5 ALBAGLI, D.; BAZAN, G.; WRIGHTON, M. S.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1992**, 114, 4150.
- 6 GAMBLE, A. S.; PATTON, J. T.; BONCELLA, J. M. *Makromol. Chem. Rapid Commun.* **1993**, 13, 109.
- 7 STANTON, C. E.; LEE, T. R.; GRUBBS, R. H.; LEWIS, N. S. *Macromolecules* **1995**, 28, 8713.
- 8 BURETEA, M. A.; TILLEY, T. D. *Organometallics* **1997**, 16, 1507.
- 9 HEO, R. W.; SOMOZA, F. B.; LEE, T. R. *J. Am. Chem. Soc.* **1998**, 120, 1621.
- 10 WATSON, K. J.; ZHU, J.; NGUYEN, S. T.; MIRKIN, C. A. *J. Am. Chem. Soc.* **1999**, 121, 462.
- 11 WATSON, K. J.; NGUYEN, S. T.; MIRKIN, C. A. *J. Organomet. Chem.* **2000**, 606, 79.
- 12 RUTJES, F. P. J. T.; SCHOEMAKER, H. E. *Tetrahedron Lett.* **1997**, 38, 677.
- 13 GARRO-HÉLION, F.; GUIBÉ, F. J. *Chem. Soc., Chem. Commun.* **1996**, 641.
- 14 LOCKE, A. J.; JONES, C.; RICHARDS, C. J. *J. Organomet. Chem.* **2001**, 637–639, 669.
- 15 OGASAWARA, M.; NAGANO, T.; HAYASHI, T. *J. Am. Chem. Soc.* **2002**, 124, 9068.
- 16 SESHADRI, H.; LOVELY, C. J. *Org. Lett.* **2000**, 2, 327.
- 17 YASUDA, T.; ABE, J.; IYODA, T.; KAWAI, T. *Chem. Lett.* **2001**, 812.
- 18 YASUDA, T.; ABE, J.; YOSHIDA, H.; IYODA, T.; KAWAI, T. *Adv. Synth. Catal.* **2002**, 344, 705.
- 19 MOHR, B.; WECK, M.; SAUVAGE, J.-P.; GRUBBS, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 1308; *Angew. Chem.* **1997**, 109, 1365.
- 20 WECK, M.; MOHR, B.; SAUVAGE, J.-P.; GRUBBS, R. H. *J. Org. Chem.* **1999**, 64, 5463.
- 21 DIETRICH-BUCHECKER, C.; RAPENNE, G.; SAUVAGE, J.-P. *J. Chem. Soc., Chem. Commun.* **1997**, 2053.
- 22 DIETRICH-BUCHECKER, C.; SAUVAGE, J.-P. *Chem. Commun.* **1999**, 615.
- 23 RAPENNE, G.; DIETRICH-BUCHECKER, C.; SAUVAGE, J.-P. *J. Am. Chem. Soc.* **1999**, 121, 994.
- 24 BELFREKH, N.; DIETRICH-BUCHECKER, C.; SAUVAGE, J.-P. *Inorg. Chem.* **2000**, 39, 5169.
- 25 DIETRICH-BUCHECKER, C. O.; SAUVAGE, J.-P. *Chem. Rev.* **1987**, 87, 795.
- 26 MARTÍN-ALVAREZ, J. M.; HAMPEL, F.; ARIF, A. M.; GLADYSZ, J. A. *Organometallics* **1999**, 18, 955.
- 27 BAUER, E. B.; RUWWE, J.; MARTÍN-ALVAREZ, J. M.; PETERS, T. B.; BOHLING, J. C.; HAMPEL, F. A.; SZAFERT, S.; LIS, T.; GLADYSZ, J. A. *Chem. Commun.* **2000**, 2261.
- 28 RUWWE, J.; MARTÍN-ALVAREZ, J. M.; HORN, C. R.; BAUER, E. B.; SZAFERT, S.; LIS, T.; HAMPEL, F.; CAGLE, P. C.; GLADYSZ, J. A. *Chem. Eur. J.* **2001**, 7, 3931.
- 29 STAHL, J.; BOHLING, J. C.; BAUER, E. B.; PETERS, T. B.; MOHR, W.; MARTÍN-ALVAREZ, J. M.; HAMPEL, F.; GLADYSZ, J. A. *Angew. Chem., Int. Ed.* **2002**, 41, 1871; *Angew. Chem.* **2002**, 114, 1951.
- 30 HORN, C. R.; MARTÍN-ALVAREZ, J. M.; GLADYSZ, J. A. *Organometallics* **2002**, 21, 5386.
- 31 BAUER, E. Doctoral Dissertation, Universität Erlangen-Nürnberg, **2003**.
- 32 MOHR, W. Doctoral Dissertation, Universität Erlangen-Nürnberg, **2002**.
- 33 PALEY, R. S.; ESTROFF, L. A.; GAUGUET, J.-M.; HUNT, D. K.; NEWLIN, R. C. *Org. Lett.* **2000**, 2, 365.
- 34 SÜLTEMAYER, J.; DÖTZ, K. H.; HUPFER, H.; NIEGER, M. *J. Organomet. Chem.* **2000**, 606, 26.
- 35 LICANDRO, E.; MAIORANA, S.; VANDONI, B.; PERDICCHIA, D.; PARAVIDINO, P.; BALDOLI, C. *Synlett* **2001**, 6, 757.
- 36 GREEN, J. R. *Synlett* **2001**, 353.

- 37 BURLISON, J. A.; GRAY, J. M.; YOUNG, D. G. J. *Tetrahedron Lett.* **2001**, 42, 5363.
- 38 MAITY, B. C.; SWAMY, V. M.; SARKAR, A. *Tetrahedron Lett.* **2001**, 42, 4373.
- 39 NG, P. L.; LAMBERT, J. N. *Synlett* **1999**, 1749.
- 40 DIJKSTRA, H. P.; CHUCHURYUKIN, A.; SUIJKERBUIJK, B. M. J. M.; VAN KLINK, G. P. M.; MILLS, A. M.; SPEK, A. L.; VAN KOTEN, G. *Adv. Synth. Catal.* **2002**, 344, 771.
- 41 POLLINO, J. M.; WECK, M. *Org. Lett.* **2002**, 4, 753.
- 42 HÜERLÄNDER, D.; KLEIGREWE, N.; KEHR, G.; ERKER, G.; FRÖHLICH, R. *Eur. J. Inorg. Chem.* **2002**, 2633.
- 43 TRNKA, T. M.; DAY, M. W.; GRUBBS, R. H. *Organometallics* **2001**, 20, 3845.
- 44 DIJKSTRA, H. P. Doctoral Dissertation, University of Utrecht, **2002**.
- 45 BAKER, M. V.; BROWN, D. H.; SKELTON, B. W.; WHITE, A. H. *Aust. J. Chem.* **2002**, 55, 655.
- 46 SATO, M.; WATANABE, M. *Chem. Commun.* **2002**, 1574.
- 47 BAUER, E. B.; SZAFERT, S.; HAMPEL, F.; GLADYSZ, J. A. *Organometallics* **2003**, 22, 2184.
- 48 TSANG, W. C. P.; JERNELIUS, J. A. J.; CORTEZ, G. A.; WEATHERHEAD, G. S.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2003**, 125, 2591, and references therein.
- 49 (a) CHAN, Y. N. C.; SCHROCK, R. R. *Chem. Mater.* **1993**, 5, 566. (b) CHAN, Y. N. C.; CRAIG, G. S. W.; SCHROCK, R. R.; COHEN, R. E. *Chem. Mater.* **1993**, 5, 885.
- 50 YUE, J.; SANKARAN, V.; COHEN, R. E.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1993**, 115, 4409.
- 51 LAEMMEL, A.-C.; COLLIN, J.-P.; SAUVAGE, J.-P.; ACCORSI, G.; ARMAROLI, N. *Eur. J. Inorg. Chem.* **2003**, 467.
- 52 MAIORANA, S.; LICANDRO, E.; PERDICCHIA, D.; BALDOLI, C.; VANDONI, B.; GIANNINI, C.; SALMAIN, M. submitted for publication.
- 53 YOUNG, D. G. J.; BURLISON, J. A.; PETERS, U. *J. Org. Chem.* **2003**, 68, 3494.
- 54 OGASAWARA, M.; NAGANO, T.; HAYASHI, T. *Organometallics* **2003**, 22, 1174.
- 55 SIERRA, J. C.; HÜERLÄNDER, D.; HILL, M.; KEHR, G.; ERKER, G.; FRÖHLICH, R. *Chem. Eur. J.* **2003**, 9, in press.
- 56 CHUCHURYUKIN, A. V.; DIJKSTRA, H. P.; SUIJKERBUIJK, B. M. J. M.; KLEIN GEBBINK, R. J. M.; VAN KLINK, G. P. M.; MILLS, A. M.; SPEK, A. L.; VAN KOTEN, G. *Angew. Chem., Int. Ed.* **2003**, 42, 228; *Angew. Chem.* **2003**, 115, 238.

2.12

Alkyne Metathesis

Alois Fürstner

2.12.1

Introduction

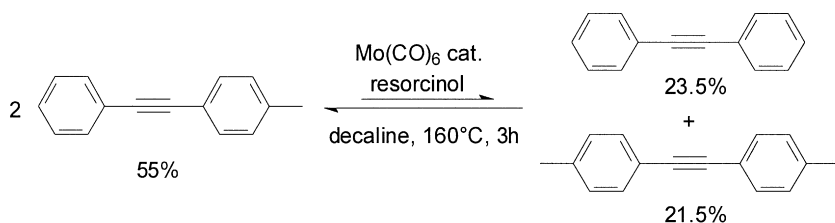
The advent of well-defined catalysts for alkene metathesis that combine high activity and durability with excellent functional group tolerance has had a tremendous impact on organic synthesis and polymer science. All the chapters of this monograph, together with a host of other pertinent literature, bear witness to this overwhelming success story [1]. With this background in mind, it seems appropriate to consider whether other metathesis reactions lend themselves to preparative purposes, since the basic principles of metathetic conversions are by no means restricted to olefins as the substrates. Summarized below is the present state of the art in alkyne metathesis. Although this reaction is still in its infancy, it shows a very promising application profile and has already borne scrutiny in target-oriented synthesis.

2.12.2

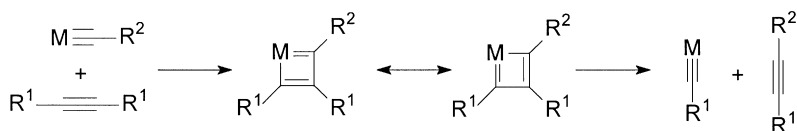
Classical Catalyst Systems for Alkyne Metathesis

Alkyne metathesis refers to the mutual exchange of the alkylidyne units between a pair of (non-terminal) acetylene derivatives [2, 3]. The first effective catalyst described in the literature consists of a heterogeneous mixture of tungsten oxides and silica that operates only at very high temperatures (ca. 200–450 °C) and is therefore hardly relevant for preparative purposes [4]. This disclosure was followed by reports of Mortreux et al. showing that homogeneous mixtures of Mo(CO)_6 (or related molybdenum sources) and simple phenol additives in high boiling solvents also effect such a scrambling process (Scheme 2.12-1) [5].

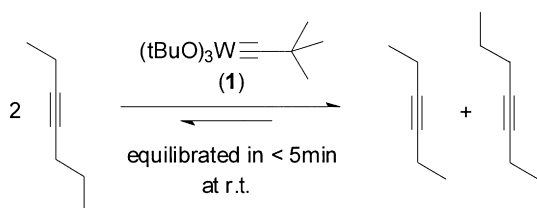
Although the nature of the catalytically active species formed *in situ* from these precursors remained elusive, Katz et al. proposed as early as 1975 that metal carbynes likely account for the catalytic turnover, triggering a sequence of formal [2+2] cycloadditions and cycloreversion steps as depicted in Scheme 2.12-2 [6, 7].



Scheme 2.12-1. First example of a homogeneously catalyzed alkyne metathesis reaction.



Scheme 2.12-2. Proposed mechanism for alkyne metathesis.



Scheme 2.12-3. Prototype alkyne metathesis catalyzed by a Schrock-type tungsten alkylidyne complex.

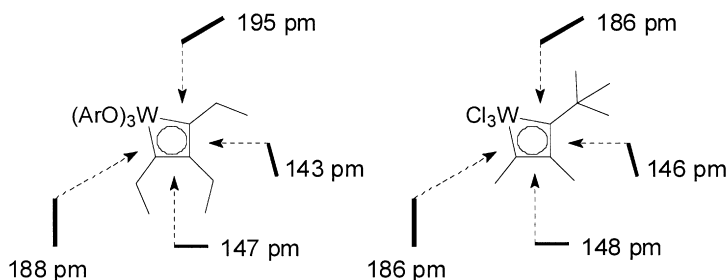
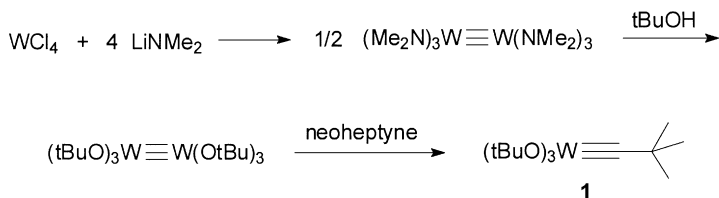


Fig. 2.12-1. Structural features of representative tungstenacyclobutadienes.

Although no “Fischer-type” carbyne has been found that allows alkyne metathesis to proceed to any sustained degree, Schrock et al. have demonstrated in a series of elegant investigations that the corresponding high valent metal alkylidyne complexes are catalytically competent and remarkably active (Scheme 2.12-3) [8]. The same group has also been able to isolate and characterize several metal-lacyclobutadiene complexes formed by [2+2] cycloaddition of alkylidyne and alkynes (Figure 2.12-1) [9]. When re-subjected to the reaction mixture, such metallocycles engender catalytic turnover, thus proving that they are competent inter-



Scheme 2.12-4. Preparation of the tungsten alkylidyne complex **1**.

mediates of the catalytic cycle as originally proposed. Moreover, it was found early on that Schrock-type alkylidynes do not readily react with alkenes [11d]. This striking pattern suggests that alkene and alkyne metatheses are orthogonal from the synthetic point of view despite the obvious mechanistic ties between these types of transformations. The preparative implications of this beneficial chemo-selective behavior, however, have been exploited only recently.

Although many different Schrock alkylidyne complexes qualify as catalysts for alkyne metathesis [8, 10], most applications are based on the use of $(\text{tBuO})_3\text{W}\equiv\text{CCMe}_3$ **1** and related species [11]. This complex can effect up to several hundred catalytic turnovers per minute and operates under fairly mild conditions; some reactions proceed even at ambient temperature. Among the different procedures for its preparation (a more comprehensive treatise of metal alkylidynes can be found in Chapter 1.11 and recent reviews [12]), the method involving the cleavage of the tungsten-tungsten triple bond of $(\text{tBuO})_3\text{W}\equiv\text{W}(\text{OtBu})_3$ [13] with neoheptyne (a process that itself represents a metathetic event) [14] is most convenient and can be carried out on a fairly large scale (Scheme 2.12-4) [11c]. The presence of bulky alkoxides as ancillary ligands to the W^{VI} center is crucial for the catalytic activity, with only minor differences being observed on replacement of $\text{tBuO}-$ with, e.g., $(\text{F}_3\text{C})_2\text{CHO}-$ [15]; the corresponding trichlorotungsten alkylidyne, $\text{Cl}_3\text{W}\equiv\text{CCMe}_3$, in contrast, is catalytically inert but can serve as a convenient starting material for the preparation of other alkylidyne complexes of this series via exchange of the $-\text{Cl}$ ligands for different alkoxides [16]. Complex **1**, which constitutes a calibration point for all studies on alkyne metathesis, is stable for extended periods of time if kept under Ar in a refrigerator.

2.12.3

Recent Advances in Catalyst Design

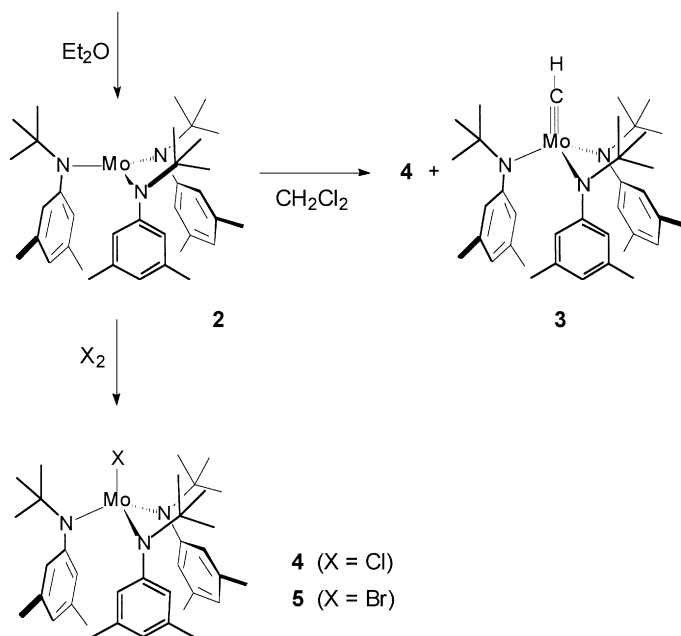
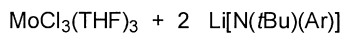
The strongly renewed interest in alkyne metathesis has triggered further studies aiming at the improvement of existing catalyst systems and/or the development of novel catalyst systems. Some investigations have been carried out with the purpose to upgrade the performance of the classical Mortreux catalysts formed from $\text{Mo}(\text{CO})_6$ and phenol additives [5]. This “instant method” is attractive for its “low-tech” character, because it requires only commercially available and shelf-stable

ingredients as well as reagent-grade solvents that must not be rigorously dried prior to use.

While the nature of the active species formed *in situ* remains unknown, spectroscopic studies suggest that the phenol component intervenes at different stages of the catalytic cycle. It is likely involved in the activation of the substrate as well as the formation of coordinatively unsaturated molybdenum species from the pre-catalyst and may also act as a pivotal ligand to the metallacyclic intermediates [5]. Therefore, the optimization of its electronic properties and acidity might result in improved catalytic performance. In fact, the use of phenols bearing electron-withdrawing substituents such as *p*-chlorophenol, *p*-trifluoromethylphenol, or *o*-fluorophenol [17–21], the adjustment of the temperature to $\approx 130^\circ\text{C}$, and the removal of released 2-butyne by purging the reaction mixture with a stream of N_2 [20] results in higher yields and reaction rates. Pre-activation of the catalyst mixture with a sacrificial alkyne such as 3-hexyne [22], the replacement of the phenol with Ph_3SiOH [23], and the use of microwave heating have also been recommended [23, 24]. The sensitivity of the catalyst prepared *in situ* towards Lewis basic functional groups, however, remains largely unchanged, and the still rather harsh conditions necessarily restrict the scope of the method to thermally robust cases. Therefore, most applications of such modified Mortreux-type catalyst systems deal with polymer synthesis; specifically, acyclic diyne metathesis (ADIMET) opens a convenient entry into poly(*p*-phenylene-ethynylenes) and related compounds with promising physical and optical properties [25, 26]. Selected applications to organic synthesis will be described below.

The only new addition to the armamentarium for alkyne metathesis made in recent years consists in the use of the sterically hindered molybdenum trisamido complex **2** as pre-catalyst (Scheme 2.12-5) [27]. This complex had originally been designed for the stoichiometric activation of N_2 and other small inorganic compounds [28]. Although **2** does not react with alkynes *per se* in hydrocarbon solvents, it is readily activated on treatment with various halogen sources; the most convenient one in practical terms is CH_2Cl_2 . The major molybdenum-containing products thus formed are the known methylidyne complex **3** [29] and the monochloro complex **4**. Although methylidyne **3** reacts with alkynes, it does not sustain catalytic turnover [27, 30]. In marked contrast, however, complex **4** and related species (e.g., the bromo analogue **5**) turned out to be powerful pre-catalysts exhibiting a remarkable tolerance towards many polar functional groups; this includes soft donors such as thioethers, amines, or crown-ether segments that are detrimental to the tungsten alkylidyne **1** (Table 2.12-1). It is believed that this excellent compatibility results from the shielding of the metal center by the bulky ligand sphere, which attenuates its effective Lewis acidity (cf. Figure 2.12-2) [27, 30].

It is unlikely that complex **4** *per se* represents the catalytically active species responsible for $\text{C}\equiv\text{C}$ bond cleavage and reassembly. The nature of the actual catalyst formed upon interaction of **4** or its precursors with an alkyne is still elusive. However, preliminary data suggest that high-valent Mo complexes might form that likely account for the observed turnover [30, 58].



Scheme 2.12-5. Preparation and activation of the molybdenum amido complex **2**.

Tab. 2.12-1. Comparison of catalysts **1** and **2**/ CH_2Cl_2 in the preparation of functionalized cycloalkynes via RCAM.

Entry	Product	Complex 1	2/ CH_2Cl_2
1		73%	91%
2		0%	84%
3		0%	88%
4		0%	60%

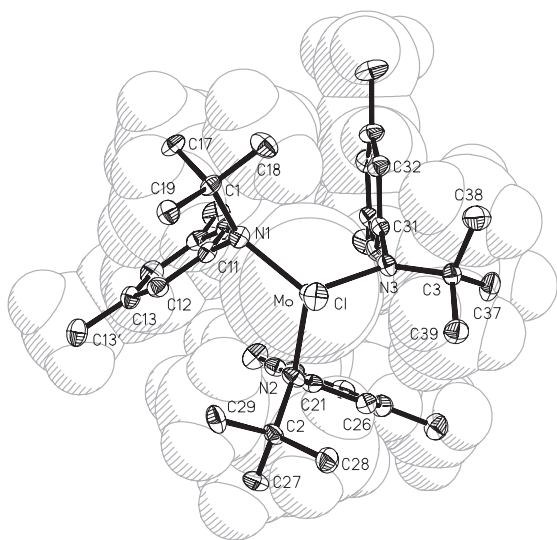


Fig. 2.12-2. Structure of complex **4** in the solid state.

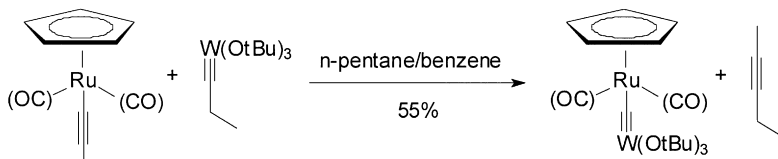
2.12.4

Preparative Applications of Alkyne Metathesis

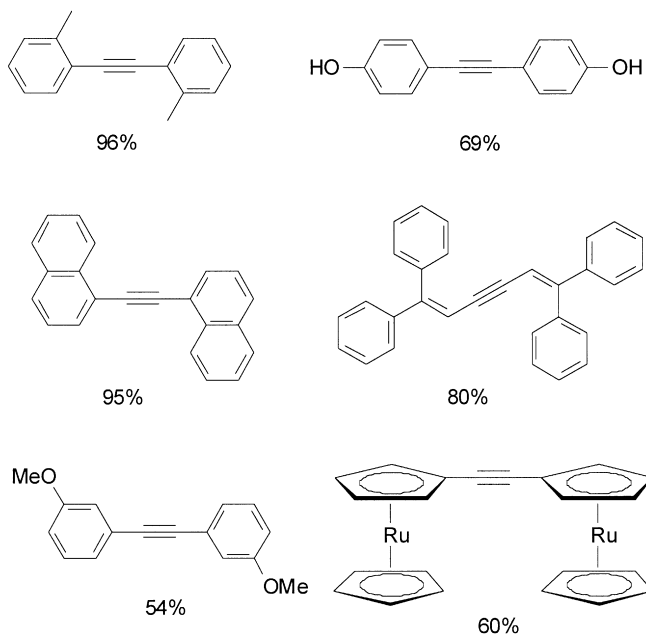
2.12.4.1

Alkyne Homometathesis Reactions

Despite the rather long history of alkyne metathesis, the availability of several catalyst systems of varying degrees of sophistication, and the fact that the essential mechanistic features of this process are well understood at the molecular level, this transformation found surprisingly little interest in the synthetic community for a long period of time. Early applications were essentially confined to either the preparation of special polymers [25, 26] or the homodimerization of barely functionalized internal alkynes. The user-friendly Mortreux system in its optimized form (i.e., *p*-ClC₆H₄OH, *p*-F₃CC₆H₄OH, *o*-FC₆H₄OH etc., Mo(CO)₆ cat.) was applied with some success to the preparation of tolane derivatives and similar products bearing ester-, ether-, silyl ether-, vinyl-, butadienyl-, styryl-, remote thienyl-, ferrocenyl-, and ruthenocyl-groups or other kinetically stable organometallic entities (Schemes 2.12-6



Scheme 2.12-6. Example of a stoichiometric alkyne metathesis reaction within the ligand sphere of a kinetically stable organometallic entity.



Scheme 2.12-7. Representative examples of products formed by alkyne homometathesis using Mortreux-type catalysts.

and 2.12-7) [17–23, 31, 32]. However, the generality is low since the position of these groups relative to the alkyne must be taken into account, with *ortho*-substituted arene derivatives being particularly problematic.

The comparison shown in Table 2.12-2 makes clear that the novel catalyst system based on $2/\text{CH}_2\text{Cl}_2$ has a significantly broader scope [33]. A variety of substrates that are beyond reach of Mortreux catalysts react without incident and provide the desired products in reasonable to good yields in all but one case.

Likewise, the Schrock alkylidyne **1** bears considerable promise due to its well-behaved reactivity and tolerance towards many polar groups [34]. The most advanced application is part of a total synthesis of dehydrohomoancepsenolide **14**, a bola-form acetogenin of marine origin bearing two butenolide rings as the head groups [35]. Its synthesis (Scheme 2.12-8) commences with an efficient zinc-induced, three-component coupling process for the formation of the diene-yne derivative **11** which cyclizes to butenolide **12** on exposure to the parent Grubbs ruthenium alkylidene complex $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$. Subsequent treatment of this compound with catalytic amounts of **1** readily affords the C_2 -symmetrical product **13**, which is reduced to the desired target by a standard Lindlar hydrogenation. The most noteworthy aspect of this synthesis is the striking chemoselectivity that becomes apparent: thus, it is possible to perform an alkene metathesis in the presence of an alkyne, followed by an alkyne metathesis which does not affect the preexisting alkene moiety. This rigorous distinction between two different types of π -bonds is important from the conceptual point of view and attests to the excellent

Tab. 2.12-2. Comparison of alkyne homometathesis reactions catalyzed by **2**/ CH_2Cl_2 or Mortreux-type systems.

Entry	Product	2 / CH_2Cl_2	$\text{Mo}(\text{CO})_6/p\text{-ClC}_6\text{H}_4\text{OH}$
1		59%	14%
2		58%	15%
3		68%	0/98% ^a
4		76%	0%
5		46%	0%
6		0%	0%

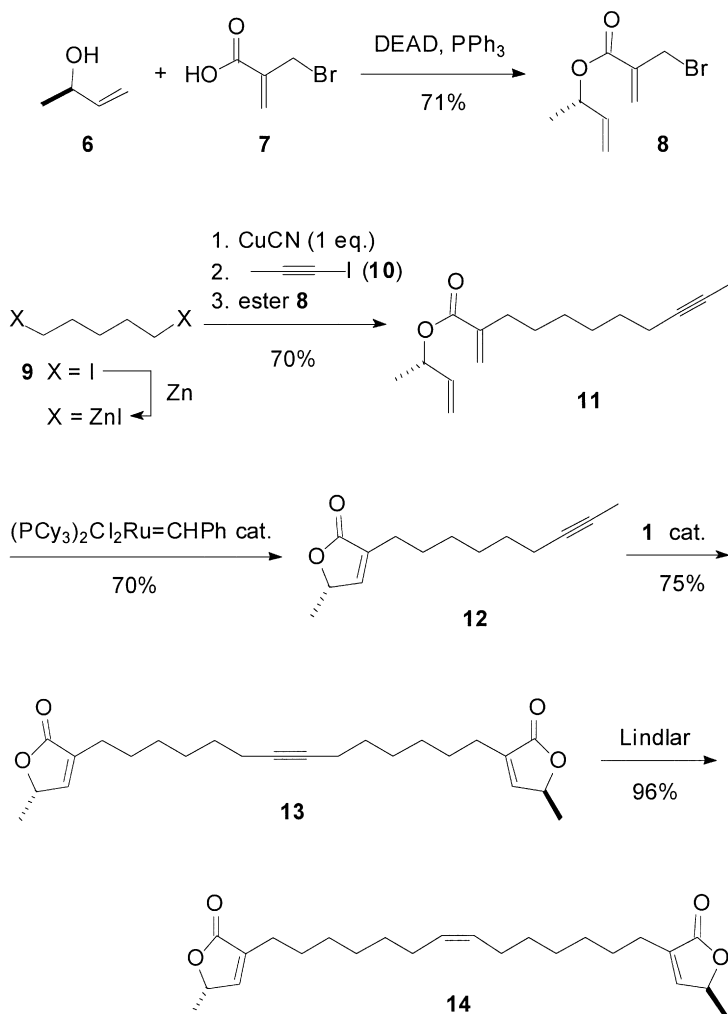
^a Using a catalyst that is pre-activated with 3-hexyne as a sacrificial alkyne.

application profile of this emerging new methodology [35]. Further examples of this selective behavior will be outlined in the following sections.

2.12.4.2

Alkyne Cross-Metathesis

The synthetic possibilities associated with alkyne cross-metathesis (ACM) were largely ignored for several decades, and only a few unsymmetrical acetylene derivatives have been prepared by this approach using the rather forcing $\text{Mo}(\text{CO})_6$ /phenol protocol [19]. Importantly, however, the novel catalyst system based on **2**/ CH_2Cl_2 gives excellent results in ACM applications [33]. Thus, a set of propynylated (hetero)arenes was cross-metathesized with a slight excess of an aliphatic alkyne as the reaction partner, which can be either symmetrical or unsymmetrical, as is evident from the data compiled in Table 2.12-3. For the first time even C-silylated alkynes qualify as the substrates that are completely unreactive under

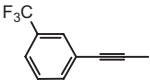
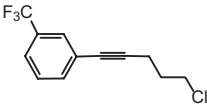
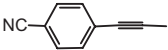
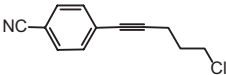
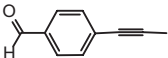
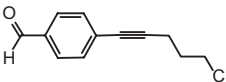
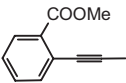
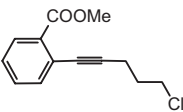
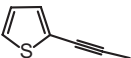

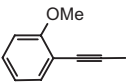
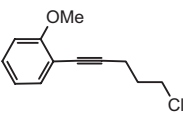
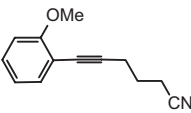
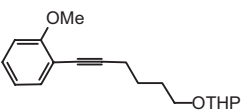
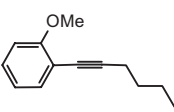

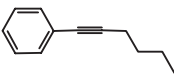


Scheme 2.12-8. Total synthesis of dehydrohomoancepsenolide **14**.

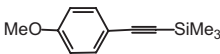
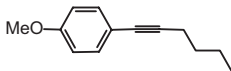
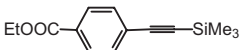
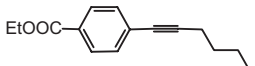
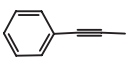
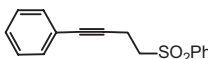
more conventional conditions and do not react even in the presence of the Schrock tungsten alkylidyne **1** (cf. entries 10–12).

The versatility of this reaction manifold is illustrated by the total synthesis of prostaglandin E_2 (PGE₂) methyl ester summarized in Scheme 2.12-9 [33]. Specifically, reaction of compound **15** containing a butynyl side chain as a handle for further elaboration with a slight excess of the symmetrical alkyne **16** in the presence of complex **2** and CH_2Cl_2 as the activating agent provides the desired ACM product **17** in 51% yield. No trace of the homodimer of substrate **15** has been detected, likely for steric reasons. Lindlar reduction of **17** followed by cleavage of the silyl-

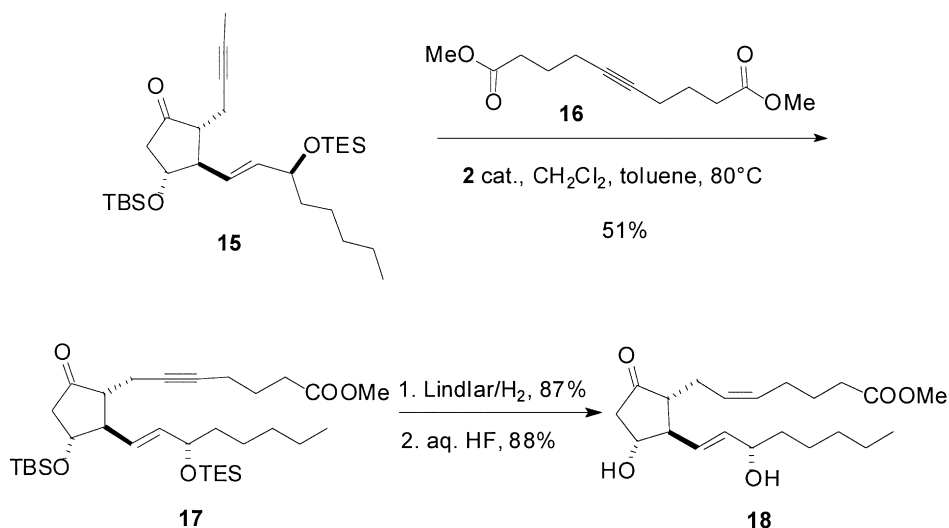
Tab. 2.12-3. Representative ACM reactions catalyzed by **2**/CH₂Cl₂.

Entry	Substrates	Product	Yield (%)
1		A 	70
2		A 	70
3		A 	47
4		A 	62
5		A 	55
6		A 	67
7		B 	82
8		C 	68
9		D 	72
10		D 	55

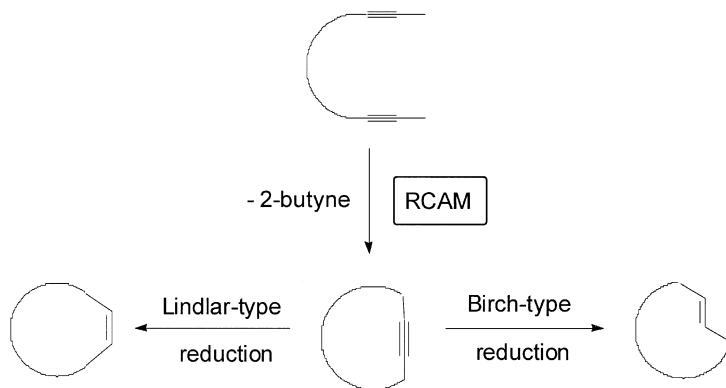
Tab. 2.12-3 (continued)

Entry	Substrates		Product	Yield (%)
11		D		60
12		D		65
13		E		71

A: 1,8-dichloro-4-octyne; B: 1,8-dicyano-4-octyne;
 C: 1,10-tetrahydropyranyloxy-5-decyne; D: 5-decyne;
 E: benzenesulfonyl-pent-3-yne.

Scheme 2.12-9. Total synthesis of PGE₂ methyl ester by ACM.

ethers under standard conditions affords PGE₂ methyl ester **18** in excellent yield, which constitutes a known precursor for free PGE₂. The compatibility of the catalyst with the preexisting alkene and the rather sensitive aldol unit residing on the cyclopentane ring of **15** are noteworthy. This favorable profile allowed the method to be extended to the preparation of a small series of PG-analogues differing from the natural products in both side chains [36]. Taken together, these examples attest to the excellent tolerance of the chosen catalyst towards polar groups and its applicability to rather labile substrates.



Scheme 2.12-10. Principle of RCAM and subsequent semi-reduction.

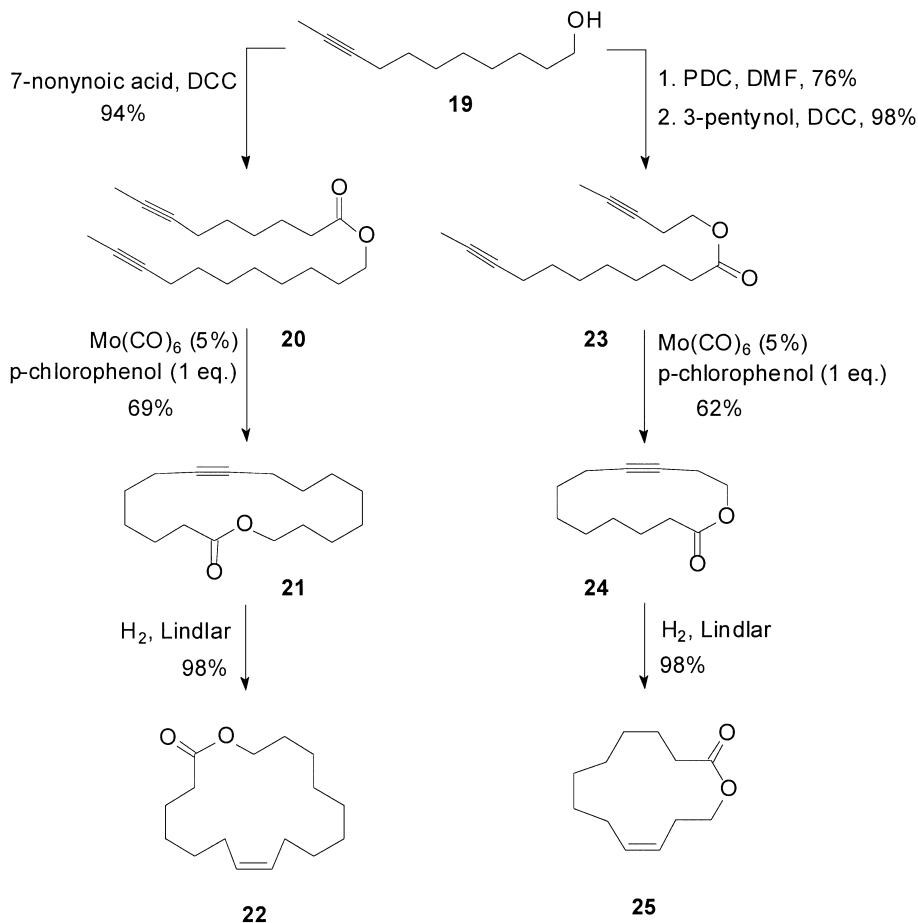
2.12.4.3

Ring-Closing Alkyne Metathesis (RCAM)

Ring-closing alkyne metathesis (RCAM) converts an acyclic diyne to a cycloalkyne that can be further elaborated into a variety of different products by suitable post-metathesis transformations [37]. Specifically, cycloalkynes serve as relays for the preparation of macrocyclic cycloalkenes of defined stereostructure if submitted to either Lindlar- or Birch-type reductions (Scheme 2.12-10).

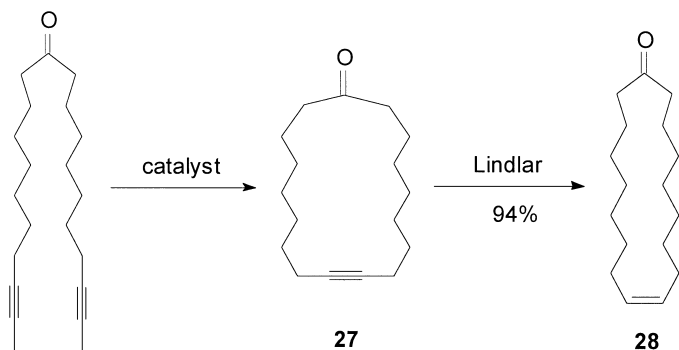
The high degree of stereocontrol inherent to this RCAM/semi-reduction manifold is a major advantage over conventional ring-closing alkene metathesis (RCM). It is well documented in the literature that RCM usually leads to mixtures of both geometrical isomers when applied to large rings, with the (*E*)-olefin dominating in many cases [1]. However, exceptions to this rule are known, and subtle changes in the substrate structure may have serious implications on the product distribution, thus making predictions rather error prone [1]. Although this problem may eventually be solved by redesigning the alkene metathesis catalysts, it presently constitutes one of the most serious shortcomings infringing upon the otherwise superb application profile of RCM.

All known catalysts for alkyne metathesis apply to RCAM, with the Mortreux-type systems being most user friendly but also most limited in terms of substrate scope. The limitations mainly derive from the harsh reaction conditions and from the sensitivity of the active species towards a variety of polar groups. Barely functionalized and thermally robust substrates, however, give excellent results using this “instant procedure” [21, 38, 39]. More specifically, this protocol in combination with conventional Lindlar reduction was successfully applied to the stereoselective synthesis of various olfactory compounds such as ambrettolide **22** [38], Yuzu lactone **25** [21, 38], and the valuable musk-scented perfume ingredient civetone **28** [40], all of which incorporate (*Z*)-alkene units into their macrocyclic rings (Schemes 2.12-11 and 2.12-12). Note that an approach to civetone based on conventional RCM, though efficient in chemical terms, mainly afforded the unnatural



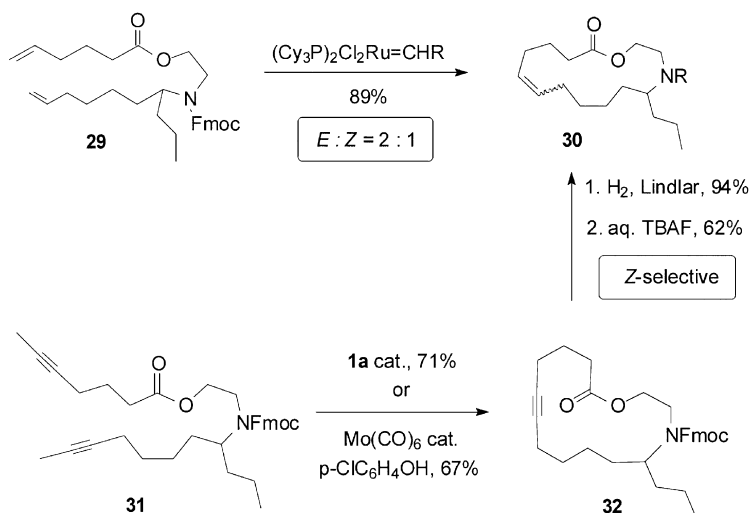
Scheme 2.12-11. Synthesis of olfactory lactones by RCAM.

(*E*)-isomer [41]. The same pertains to syntheses of epilachnene (*Z*-**30**) and homologues thereof, insect repellent alkaloids isolated from the larvae of the Mexican beetle *Epilachna varivestis*. While conventional RCM of diene **29** gives a 2:1 mixture of both geometrical isomers, with the undesired (*E*)-olefin being favored [41], alkyne metathesis of substrate **31** followed by Lindlar reduction of the resulting cycloalkyne **32** accounts for a fully stereoselective route to this unusual alkaloid (Scheme 2.12-13) [38]. Along similar lines, a concise entry into the promising cytotoxic marine natural product motuporamine C **39** has been developed, which again is distinguished by the stereoselective formation of the (*Z*)-configured 15-membered cycloalkene via RCAM/Lindlar (Scheme 2.12-14) [42]. Therefore, this route compares favorably to an alternative synthesis of this alkaloid based on RCM, which is less appealing from the preparative point of view, as it leads to a mixture of both isomers that is difficult to separate [43].



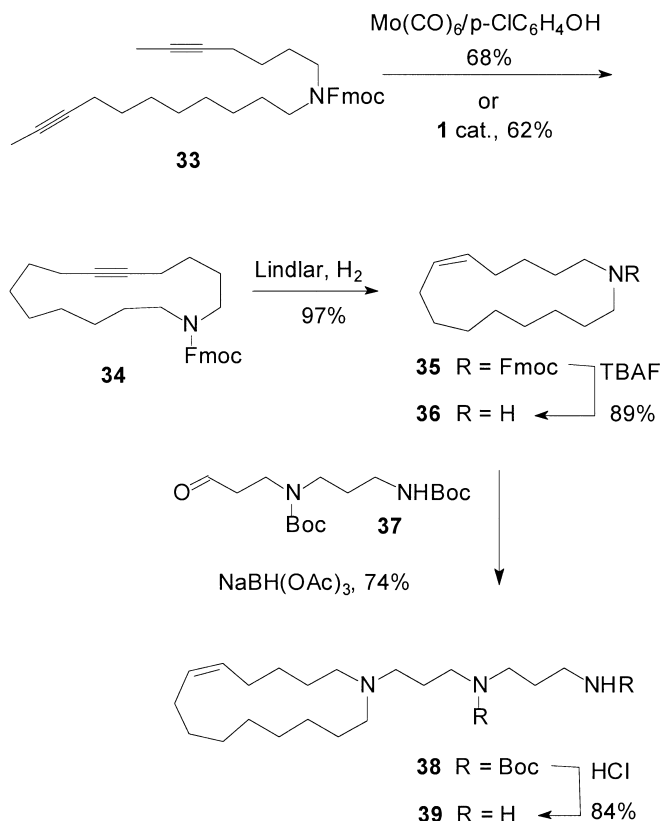
catalyst	yield
$\text{Mo}(\text{CO})_6 / \text{F}_3\text{CC}_6\text{H}_4\text{OH}$	59%
$(\text{tBuO})_3\text{WCCMe}_3$ (1)	65%
$[(\text{tBu})(\text{Ar})\text{N}]_3\text{Mo}$ (2) / CH_2Cl_2	70%

Scheme 2.12-12. Stereoselective synthesis of civetone by RCAM.



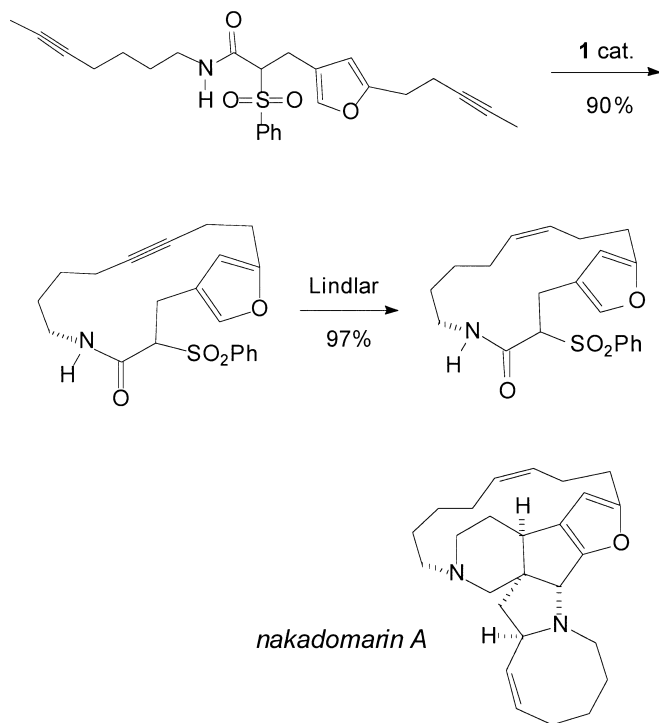
Scheme 2.12-13. Synthesis of epilachnene **30** ($\text{R} = \text{H}$). Comparison of the RCM- and RCAM-based approaches.

To explore the full scope of RCAM, however, it is necessary to employ either Schrock-type alkyldiyne complexes such as **1** and congeners or the newly developed catalyst system based on **2**/ CH_2Cl_2 . These systems exhibit not only a greater performance in most instances but also a significantly enhanced tolerance towards

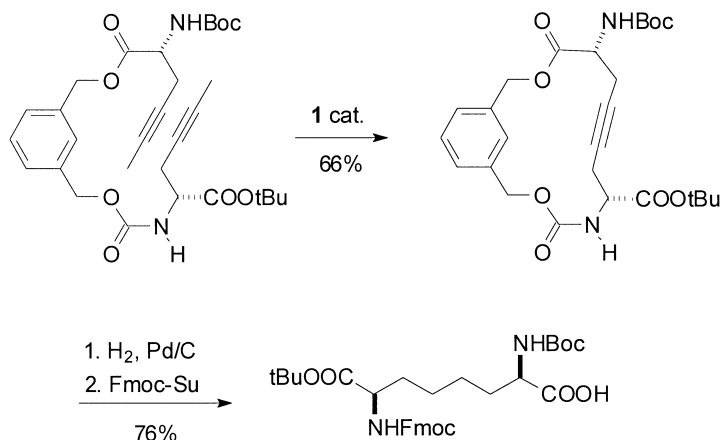


Scheme 2.12-14. Synthesis of motuporamine **C 39** by RCAM.

functional groups. The latter aspect is evident from a model study directed at the macrocyclic perimeter of nakadomarin A (Scheme 2.12-15) [38] as well as from a series of cyclization reactions leading to the formation of various peptide isosteres (cf. Scheme 2.12-16) [44]. These RCAM reactions proceed with high reaction rates that usually surpass those of comparable RCM processes catalyzed by the standard ruthenium complexes; in no case have cycloallenes or other conceivable products derived from isomerization of the alkyne units been observed as byproducts. Limitations for RCAM, however, are encountered with electron-deficient alkynes such as butynoates [38]. Moreover, the tungsten alkylidyne **1** is sensitive to soft Lewis donors such as thioethers or amines in the substrates (cf. Table 2.12-1) [38], whereas the basic ligands present in the **2**/ CH_2Cl_2 system require all acidic sites in the substrates (including even secondary amides) to be properly protected [27, 30]. So far, the smallest ring formed by RCAM is an 11-membered cycloalkyne, although a significant amount of the corresponding cyclodimer was observed as a byproduct in this particular case [30].



Scheme 2.12-15. Model study concerning the synthesis of the macrocyclic ring of nakadomarin A.



Scheme 2.12-16. RCAM-based synthesis of a peptide isostere.

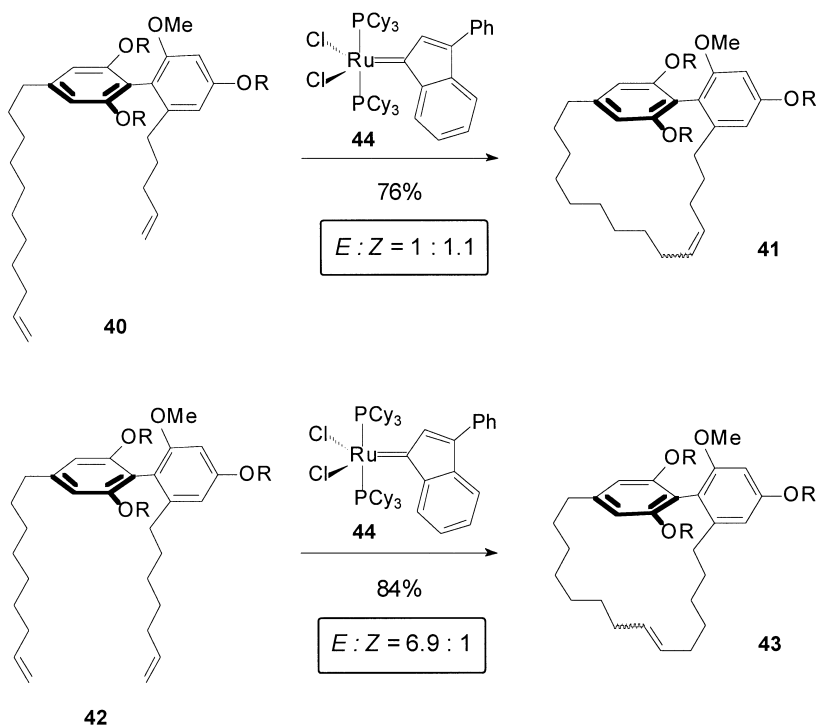
2.12.4.4

Applications of RCAM to Natural Product Synthesis

Turrianes

The recent total syntheses of two members of the turriane family, naturally occurring cyclophane derivatives endowed with DNA-cleaving properties under oxidative conditions, illustrates many chemical features of metathesis chemistry. Specifically, it provides a direct comparison between RCM and RCAM as well as between different catalyst systems [24].

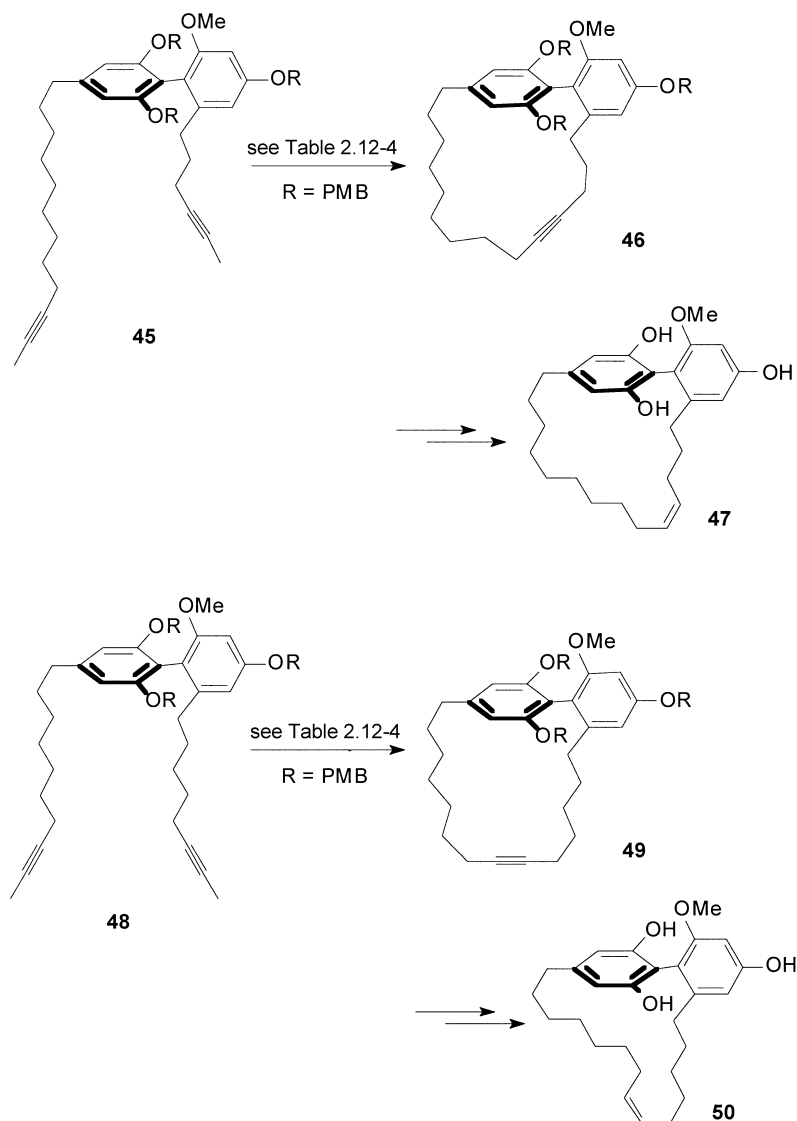
Specifically, a set of suitable substrates bearing either alkene or alkyne moieties at the appropriate positions has been synthesized by an efficient route that relies on oxazoline chemistry for the construction of the sterically hindered 2,2',6,6'-tetrasubstituted biaryl unit and benzylic alkylation strategies for the attachment of the lateral chains. Dienes **40** and **42** thus formed, on treatment with the ruthenium indenylidene complex **44** as a particularly well-accessible alternative to the classical Grubbs catalyst [45], cyclize without incident to the desired macrocyclic rings **41** and **43**, respectively (Scheme 2.12-17). Not unexpectedly, however, mixtures of both stereoisomers are formed that are difficult to separate even by preparative HPLC. The fact that cycloalkene **41** is obtained as an *E:Z* = 1:1.1 mixture, whereas its congener **43** shows an *E:Z* = 6.9:1 ratio, illustrates the subtle influence of the site



Scheme 2.12-17. Synthesis of turriane derivatives by RCM.

of ring closure on the stereochemical outcome of RCM. Although this relationship *per se* may not come as a surprise, it remains difficult to date to predict the stereochemical course of such RCM-based macrocyclization reactions with any degree of certainty. Since alkyne metathesis allows the formation of the desired olefin geometry in a stereoselective and predictable manner, it is the method of choice en route to targets of this type.

In fact, cyclization of the corresponding diynes **45** and **48** proceeds with good chemical yields independent of the chosen catalyst system (Scheme 2.12-18 and



Scheme 2.12-18. Stereoselective synthesis of turrianes **47** and **50** via RCAM.

Tab. 2.12-4. Formation of the turriane precursors by RCAM.

Nr	Substr.	Catalyst	Conditions ^a	Time	Product	Yield
1	45	(<i>t</i> -BuO) ₃ W≡CCMe ₃	A	16 h	46	64%
2	45	Mo(CO) ₆ , F ₃ CC ₆ H ₄ OH	B	4 h	46	83%
3	45	Mo(CO) ₆ , F ₃ CC ₆ H ₄ OH	C	5 min	46	69%
4	48	(<i>t</i> -BuO) ₃ W≡CCMe ₃	A	16 h	49	61%
5	48	Mo(CO) ₆ , F ₃ CC ₆ H ₄ OH	B	6 h	49	76%
6	48	Mo(CO) ₆ , F ₃ CC ₆ H ₄ OH	C	5 min	49	71%

^a A: toluene, 80 °C; B: chlorobenzene, 135 °C; C: chlorobenzene, 150 °C, microwave heating.

Table 2.12-4) [24]. Due to the thermal stability of the products and the fact that only robust protecting groups are present, even the convenient *in situ* system (Mo(CO)₆/F₃CC₆H₄OH) can be applied; in this case it is remarkable to that the rate of the reaction can be increased by the application of microwave technology instead of conventional heating, thus allowing us to reduce the overall reaction time from 6 h to 5 min (cf. Table 2.12-4, entries 5 and 6). The generality of this observation, however, remains to be explored [46]. Lindlar reduction of **46** and **49** followed by cleavage of the PMB groups completes the first total synthesis of the naturally occurring cyclophane derivatives **47** and **50**, respectively.

Sophorolipid lactone

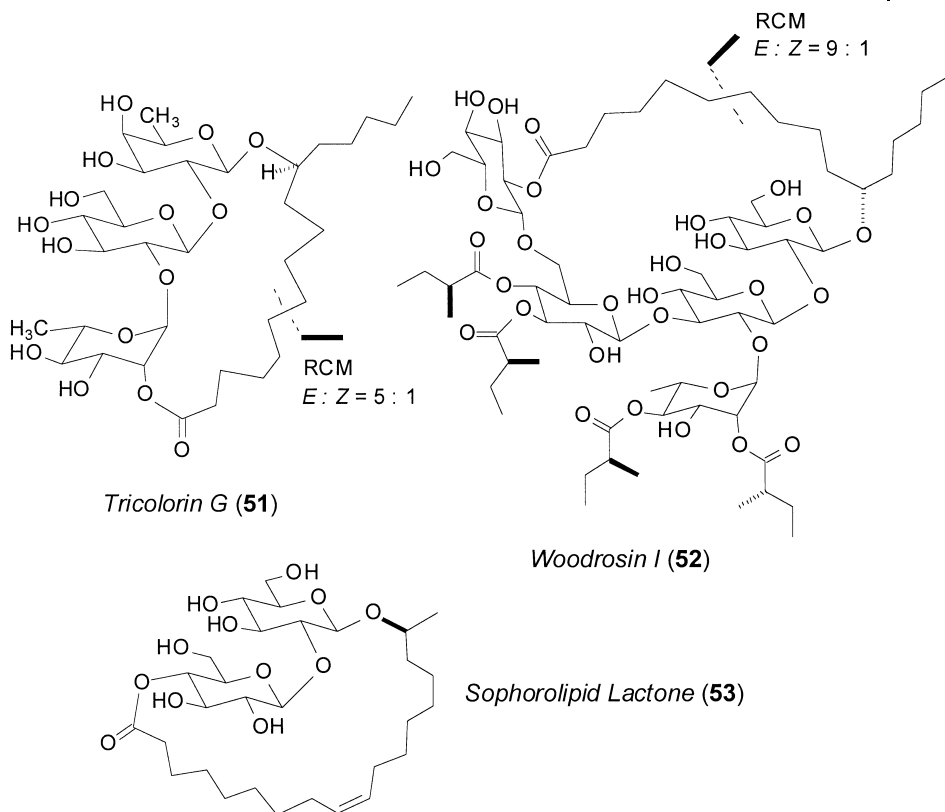
RCM has been applied with considerable success to the formation of bioactive resin glycosides, a conspicuous class of glycoconjugates containing a fatty acid moiety spanning several sugars of their oligosaccharide backbones [47]. In all cases, however, mixtures of both stereoisomeric alkenes have been formed upon closure of the macrocycle, with the (*E*)-alkenes prevailing (cf. Scheme 2.12-19). This outcome was inconsequential, as the olefins were reduced during later stages of the syntheses of compounds such as tricolorin G **51** or woodrosin I **52**.

In view of this precedence, however, it seemed highly unlikely that sophorolipid lactone **53**, a close relative containing a (*Z*)-olefin in its lipidic tether, could be formed by RCM with any reasonable degree of selectivity. Therefore a route based on RCAM was chosen, the key steps of which are shown in Scheme 2.12-20 [48].

Specifically, diyne **54**, which is available in a few operations from standard carbohydrate building blocks, upon exposure to the newly developed catalyst system based on 2/CH₂Cl₂, delivers the desired cycloalkyne **55** in 78% isolated yield. Subsequent Lindlar reduction followed by oxidative cleavage of the PMB-ether groups completes the stereoselective synthesis of this demanding target [48].

Prostaglandin lactones

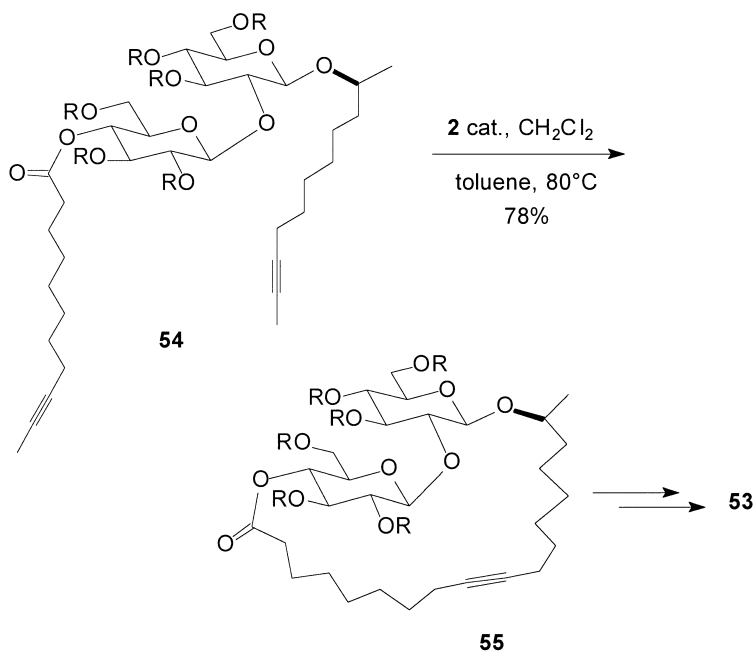
The total synthesis of prostaglandin E₂-1,15-lactone (PGE₂ lactone) **59** and analogues thereof constitutes an even more stringent test for the performance of the novel alkyne metathesis catalysts [36, 49]. These unusual natural products of



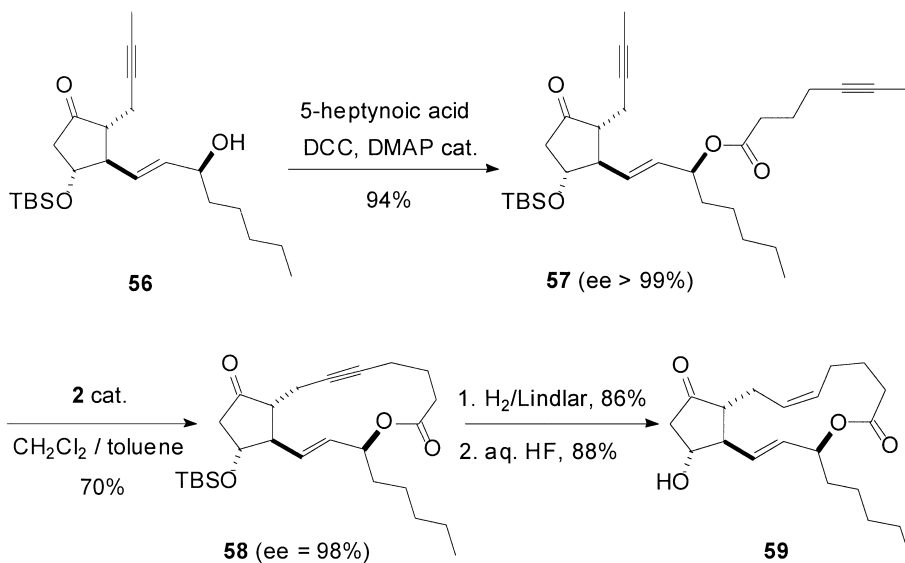
Scheme 2.12-19. Representative examples of resin glycosides.

marine origin isolated from the nudibranch *Tethys fimbria* are readily saponified by hydrolytic enzymes and therefore constitute attractive pro-drugs for the parent prostaglandins. The labile aldol moiety residing on the cyclopentane ring, which is equally susceptible to acid and base, together with the rather electrophilic ketone moiety and the preexisting alkene in the ω side chain, render this target an attractive testing ground for RCAM.

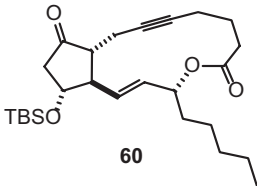
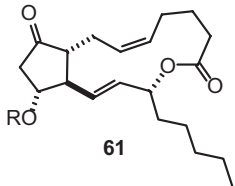
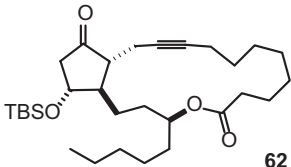
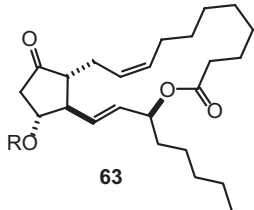
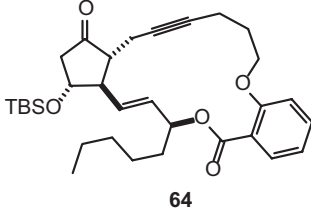
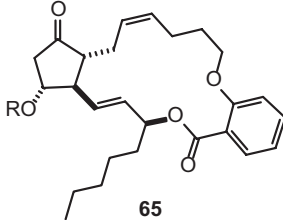
The required metathesis precursor **57** is formed from compound **56** (readily available by standard three-component coupling) by esterification with 5-heptynoic acid (Scheme 2.12-21). Its transformation to the desired cycloalkyne **58** proceeds in good yield in the presence of **2**/ CH_2Cl_2 in toluene at 80 °C. It is remarkable that this catalyst system rigorously distinguishes between different π systems, since it reacts exclusively with the triple bond, while the olefin in the substrate remains untouched. Moreover, all labile structural elements are preserved, as is the integrity of the chiral center α to the carbonyl. Lindlar reduction of cycloalkyne **58** followed by deprotection of the residual TBS ether completes the total synthesis of PGE_2 -lactone **59** [36, 49]. Because the hydrolysis of **59** to the parent PGE_2 has previously



Scheme 2.12-20. Key step of a total synthesis of sophorolipid lactone.

Scheme 2.12-21. Total synthesis of prostaglandin E_2 1,15-lactone.

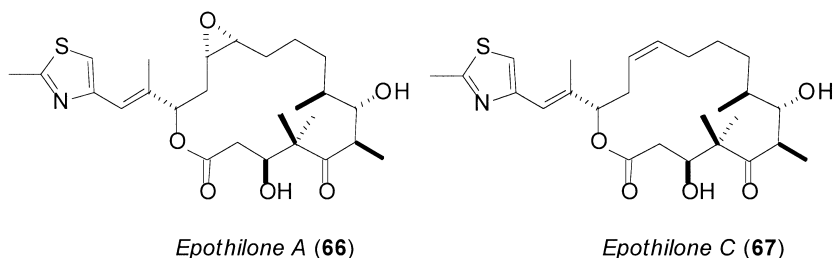
Tab. 2.12-5. Synthesis of prostaglandin lactone analogues by RCAM/Lindlar hydrogenation.

Catalyst	Product	Yield	PG-analogue
$[(t\text{Bu})(\text{Ar})\text{N}]_3\text{Mo}^{a,b}$ $[(t\text{Bu})(\text{Ar})\text{N}]_3\text{Mo}^{a,c}$ $(t\text{BuO})_3\text{W}\equiv\text{CCMe}_3$ (1) $\text{Mo}(\text{CO})_6/p\text{-ClC}_6\text{H}_4\text{OH}$	 60	81% 87% 65% 0%	 61
$[(t\text{Bu})(\text{Ar})\text{N}]_3\text{Mo}^{a,c}$	 62	63%	 63
$[(t\text{Bu})(\text{Ar})\text{N}]_3\text{Mo}^{a,c}$	 64	86%	 65

^a Pre-activated with CH_2Cl_2 .^b Ar = 3,5-dimethylphenyl.^c Ar = 4-fluorophenyl.

been described in the literature, this approach constitutes a formal total synthesis of this bioactive compound as well.

A major strategic advantage associated with any metathesis reaction is its inherent flexibility. This aspect is illustrated by the synthesis of three PGE analogues compiled in Table 2.12-5, all of which derive from the same precursor **56** [36]. The RCAM step is invariably highly productive, delivering the desired cycloalkynes **60**, **62**, and **64** in good to excellent yields. Moreover, a direct comparison of the different alkyne metathesis catalysts provides additional information: while the two $[(t\text{Bu})(\text{Ar})\text{N}]_3\text{Mo}/\text{CH}_2\text{Cl}_2$ systems tested (Ar = 3,5-dimethylphenyl or 4-fluorophenyl) perform exquisitely well and the tungsten alkylidyne **1** also gives respectable results, Mortreux's instant method fails completely, as the substrate does not withstand the thermal stress necessary in this case [36].



Scheme 2.12-22. Structures of epothilone A and C.

Epothilone A and C

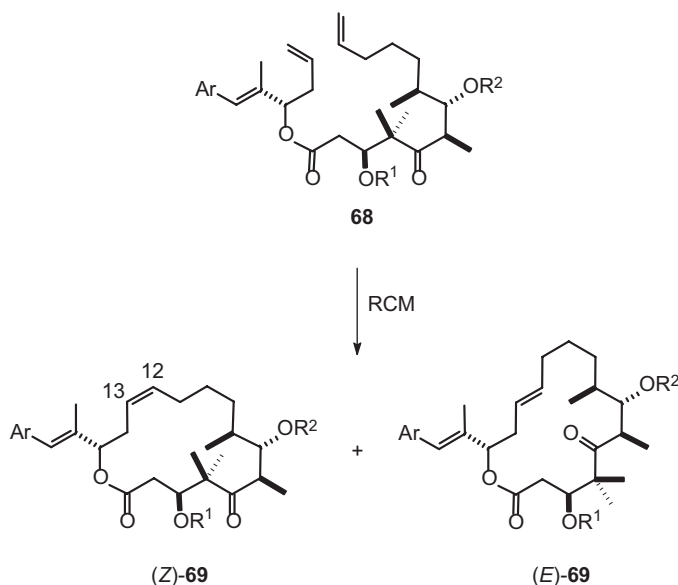
The discovery that epothilone A **66** and congeners (Scheme 2.12-22) share a common mechanism of action with the approved anticancer drug paclitaxel (Taxol[®]) but retain high activity even against paclitaxel-resistant human cancer cell lines *in vitro* has spurred considerable drug-development programs worldwide. As a consequence, these compounds became the focal point of many preparative studies aiming at their total synthesis and a synthesis-driven mapping of their structure-activity profile [50].

In this context it is remarkable that the first three successful entries into the epothilone series were all based on ring-closing alkene metathesis (RCM) for the formation of the 16-membered core [51–53]. Product (Z)-**69** thus formed can be selectively epoxidized at the $\Delta^{12,13}$ bond and hence constitutes an excellent precursor for epothilone A **66**. Although these studies were early highlights showing the potential of RCM for advanced organic synthesis, they invariably suffered from the fact that there was little, if any, selectivity in favor of the required (Z)-alkene (Z)-**69** (Table 2.12-6). Because this serious problem arose only towards the very end of rather laborious sequences and because the isomeric alkenes could not be readily separated at this stage, it is hardly surprising that subsequent total syntheses of **66** were based largely on strategies other than RCM that ensure better control over all structural elements of this target [50].

These aspects, however, render the epothilones a particularly suitable and relevant testing ground to probe our concept of the stereoselective preparation of (Z)-alkenes via RCAM followed by Lindlar reduction. Moreover, the presence of a basic N- as well as an S-atom in their thiazole ring provides a stringent test for the functional group tolerance of the novel molybdenum-based catalyst **2**/CH₂Cl₂.

The key steps of our stereoselective approach to this promising target are summarized in Scheme 2.12-23 [30, 54]. The three building blocks **70–72**, each of which is accessible by a high yielding route based largely on the use of transition metal chemistry, are assembled in a straightforward manner to diyne **73**, which sets the basis for the envisaged ring closure. Gratifyingly, this substrate is smoothly converted to the 16-membered cycloalkyne **74** in 80% isolated yield on exposure to catalytic amounts of the molybdenum amido complex **2** in toluene/CH₂Cl₂ at 80 °C. This outcome is particularly noteworthy, as it compares well to the results obtained in the conventional RCM approaches (Table 2.12-6) in terms of yield and

Tab. 2.12-6. RCM approaches towards epothilone A and C: Cyclization of dienes **68** invariably leads to the formation of (*E*, *Z*)-mixtures of cycloalkene **69** (Ar = 2-methyl-4-thiazolyl).



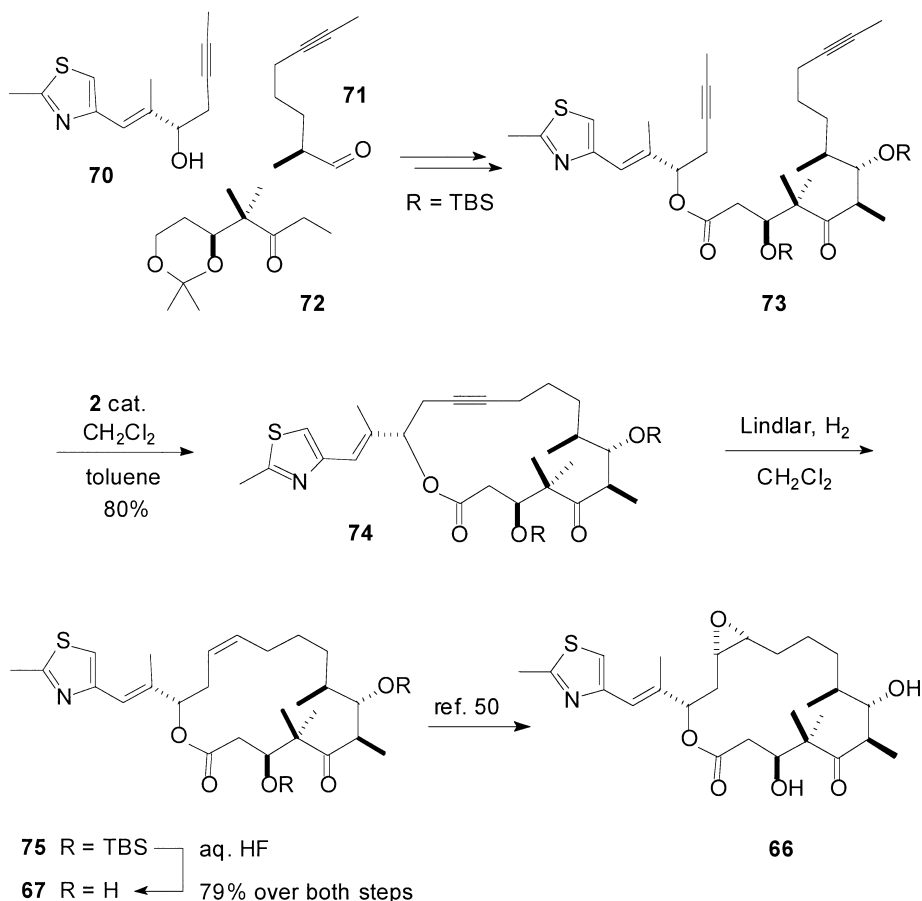
Catalyst ^a	R ¹	R ²	Yield (%)	Z:E
[Ru] ^a	TBS	TBS	86	1.7:1
	TBS	TBS	94	1:1
	TBS	TBS	81–85	1.5:1
	TBS	H	85	1.2:1
	H	H	65	1:2
[Mo] ^b	TBS	TBS	86	1:2

^a[Ru] = (PCy₃)₂(Cl)₂Ru=CHPh.

^b[Mo] = Mo(=NAr)(=CHCMe₂Ph)[OCMe(CF₃)₂]₂.

reaction rate. Furthermore, it clearly attests to the mildness and preparative relevance of the RCAM method since (1) neither the basic N-atom nor the sulfur group of the thiazole ring interferes with the catalyst; (2) the labile aldol substructure, the rather electrophilic ketone, as well as the ester and silyl ether groups are fully preserved; (3) no racemization of the chiral center α to the carbonyl is encountered; and (4) the rigorous chemoselectivity of the catalyst is confirmed, which reacts smoothly with alkynes but leaves preexisting alkene moieties unaffected. Therefore, this particular example in concert with the other applications summarized above substantiate the notion that alkyne metathesis in general holds great promise for target-oriented synthesis.

Lindlar reduction of cycloalkyne **74** followed by cleavage of the silyl ether groups in the resulting (*Z*)-alkene **75** by means of aq. HF in Et₂O/MeCN delivers epothilone C **67** in 79% yield. Because the selective epoxidation of **75** has already been



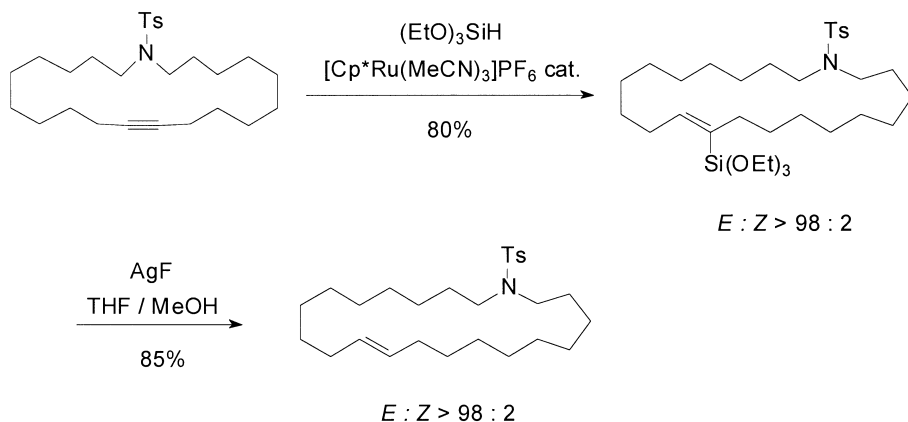
Scheme 2.12-23. Stereoselective total synthesis of epothilone A and C based on RCAM.

described by various groups, this approach constitutes a formal total synthesis of epothilone A **66** as well [30, 54].

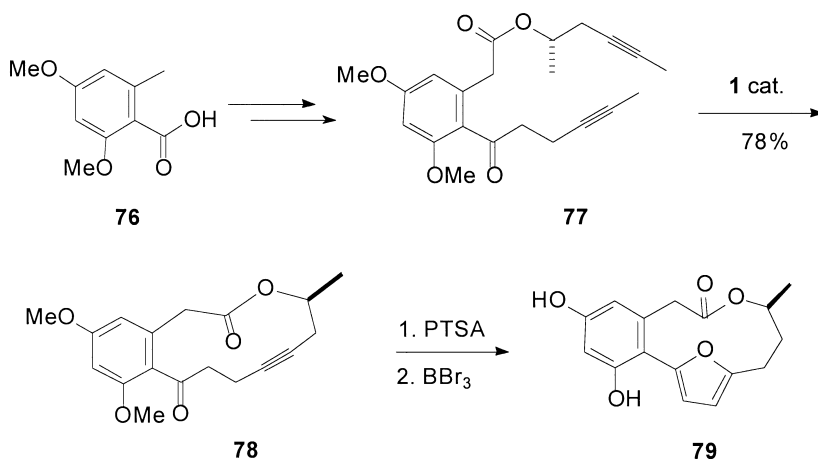
2.12.4.5

Post-Metathesis Transformations Other Than Lindlar Hydrogenation: Selective Synthesis of (*E*)-Alkenes and Heterocyclic Motifs

While the utility of the RCAM/Lindlar manifold for the stereoselective formation of (*Z*)-configured cycloalkenes is firmly established, the complementary semi-reduction of cycloalkynes to the corresponding (*E*)-alkenes has received much less attention. This may be attributed in part to the fact that known methodology for this transformation is less attractive because it requires the use of either dissolving metals in liquid ammonia or an excess of toxic Cr(II) salts. Recently, however, a new procedure has been described that may fill this gap. It consists of a ruthenium-catalyzed *trans*-selective hydrosilylation followed by a proto-desilylation



Scheme 2.12-24. Chemo- and stereoselective reduction of cycloalkynes to (*E*)-alkenes.



Scheme 2.12-25. Key steps of a total synthesis of citreofuran **79**.

of the resulting vinylsilanes mediated by AgF (Scheme 2.12-24) [55, 56]. This method is compatible with many functional groups and therefore holds promise for applications to advanced organic synthesis.

Yet other ways to elaborate the cycloalkynes formed by RCAM via suitable post-metathesis transformations remain to be explored. In addition to the obvious possibilities associated with cycloaddition, oxidation, or skeletal rearrangement reactions, cycloalkynes are known to encode for various heterocyclic motifs. The total synthesis of citreofuran **79**, a secondary metabolite of *Penicillium citreo-viride*, serves as an illustration of this concept (Scheme 2.12-25) [57]. Specifically, the readily available orsellinic acid derivative **76** is converted in a few steps to diyne **77**, which undergoes efficient ring closure on treatment with catalytic amounts of the tungsten alkylidyne **1**. Exposure of the resulting cycloalkyne **78** to *p*-toluenesulfonic acid in toluene renders its somewhat strained triple bond sus-

ceptible to nucleophilic attack by the adjacent carbonyl group, thereby leading to the desired 2,5-disubstituted furan ring embedded into the macrocyclic skeleton of this natural product. Final cleavage of the methyl ether groups completes the first total synthesis of citreofuran **79** [57].

2.12.5

Conclusions and Outlook

Although alkyne metathesis *per se* is a fairly old reaction, it is only recently gaining importance for preparative organic chemistry. Three catalyst systems are known to date that show significant differences with regard to practicality and scope. While the “instant procedure” pioneered by Mortreux (i.e., $\text{Mo}(\text{CO})_6$ and phenols) is particularly easy to use, it requires high reaction temperatures that may be detrimental to elaborate substrates; moreover, the sensitivity of the catalytically active species formed *in situ* against many polar substituents severely restricts the applicability of this system. In contrast, the well-defined tungsten complex **1** and related alkylidyne species as well as a newly developed catalyst system based on $[(t\text{Bu})(\text{Ar})\text{N}]_3\text{Mo}$ **2** operate under mild conditions and are distinguished by an excellent functional group tolerance, as can be seen from Table 2.12-7; they are, however, more sensitive in terms of handling.

Tab. 2.12-7. Functional groups known to be compatible with the alkyne metathesis catalysts **1** and **2**/ CH_2Cl_2 .

2 / CH_2Cl_2	1
Acetal	Acetal
Aldehyde	
Alkene	Alkene
Alkyl chloride	
tert-Amide	Amide
Enoate	Enoate
Ester	Ester
Ether	Ether
	Furan
Glycoside	
Ketone	Ketone
Nitrile	
Nitro	
Pyridine	
Silyl ether	Silyl ether
Sulfonamide	Sulfonamide
Sulfone	Sulfone
Thiazole	
Thioether	
Urethane	Urethane

A series of total syntheses of natural products based on alkyne homometathesis, ACM, or RCAM illustrates the preparative relevance of this type of transformation. Its utilitarian potential likely will increase further as the available catalyst systems become better understood, more tunable, and more user friendly. Thereby, a reaction sequence comprising RCAM followed by either a Lindlar- or a Birch-type semi-reduction of the cycloalkynes initially formed deserves particular mentioning, because it provides a stereoselective entry into macrocyclic cycloalkenes with a defined and predictable configuration of the double bond. Since this methodology complements contemporary alkene metathesis chemistry, the alkyne metathesis/semi-reduction manifold is expected to find further applications in target-oriented synthesis [59].

References

- 1 a) T. M. TRNKA, R. H. GRUBBS, *Acc. Chem. Res.* **2001**, *34*, 18; b) A. FÜRSTNER, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; c) R. H. GRUBBS, S. CHANG, *Tetrahedron* **1998**, *54*, 4413; d) M. SCHUSTER, S. BLECHERT, *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2037; e) A. FÜRSTNER, *Top. Catal.* **1997**, *4*, 285; f) S. K. ARMSTRONG, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371; g) K. J. IVIN, *J. Mol. Catal. A: Chem.* **1998**, *133*, 1; h) M. L. RANDALL, M. L. SNAPPER, *J. Mol. Catal. A: Chem.* **1998**, *133*, 29; i) R. R. SCHROCK, *Tetrahedron* **1999**, *55*, 8141; j) M. E. MAIER, *Angew. Chem.* **2000**, *112*, 2153; *Angew. Chem. Int. Ed.* **2000**, *39*, 2073.
- 2 Short reviews: a) ref. [1b]; b) U. H. F. BUNZ, L. KLOPPENBURG, *Angew. Chem.* **1999**, *111*, 503; *Angew. Chem. Int. Ed.* **1999**, *38*, 478; c) T. LINDEL, *Nachr. Chem.* **2000**, *48*, 1242; d) A.-B. ZHANG, H. GONG, S.-M. MA, *Chin. J. Org. Chem.* **2001**, *21*, 541.
- 3 Terminal alkynes deactivate the known catalysts and are prone to polymerization under the reaction conditions, cf. a) A. BRAY, A. MORTREUX, F. PETIT, M. PETIT, T. SZYMANSKA-BUZAR, *J. Chem. Soc. Chem. Commun.* **1993**, 197; b) A. MORTREUX, F. PETIT, M. PETIT, T. SZYMANSKA-BUZAR, *J. Mol. Catal. A: Chem.* **1995**, *96*, 95; see also: c) P. R. SHARP, S. J. HOLMES, R. R. SCHROCK, M. R. CHURCHILL, H. J. WASSERMAN, *J. Am. Chem. Soc.* **1981**, *103*, 965.
- 4 a) F. PENNELLA, R. L. BANKS, G. C. BAILEY, *Chem. Comm.* **1968**, 1548; for further publications on heterogeneous catalysts for alkyne metathesis see: b) A. MORTREUX, M. BLANCHARD, *Bull. Soc. Chim. Fr.* **1972**, 1641; c) J. A. MOULIJN, H. J. REITSMA, C. BOELHOUWER, *J. Catal.* **1972**, *25*, 434; d) A. MORTREUX, F. PETIT, M. BLANCHARD, *J. Mol. Catal.* **1980**, *8*, 97.
- 5 a) A. MORTREUX, M. BLANCHARD, *J. Chem. Soc. Chem. Comm.* **1974**, 786; b) A. MORTREUX, N. DY, M. BLANCHARD, *J. Mol. Catal.* **1975/76**, *1*, 101; c) A. MORTREUX, F. PETIT, M. BLANCHARD, *Tetrahedron Lett.* **1978**, 4967; d) A. BENICHEICK, M. PETIT, A. MORTREUX, F. PETIT, *J. Mol. Catal.* **1982**, *15*, 93; e) A. MORTREUX, J. C. DELGRANGE, M. BLANCHARD, B. LUBOCHINSKY, *J. Mol. Catal.* **1977**, *2*, 73.
- 6 T. J. KATZ, J. MCGINNIS, *J. Am. Chem. Soc.* **1975**, *97*, 1592.
- 7 Later on, it has been speculated if other mechanistic pathways might be operative involving either metalla-tetrahedranes (cf. ref. [11d]) or metallacyclopentadienes (cf. ref. [19]) as the catalytically relevant intermediates. These proposals, however, have not been corroborated and the [2+2] cycloaddition/cycloreversion pathway now seems to be generally accepted. For a computational study on the mechanism of alkyne metathesis suggesting that metallatetrahedranes are likely unreactive sinks

- rather than catalytically competent species see: T. WOO, E. FOIGA, T. ZIEGLER, *Organometallics* **1993**, *12*, 1289.
- 8 a) J. H. WENGROVIUS, J. SANCHO, R. R. SCHROCK, *J. Am. Chem. Soc.* **1981**, *103*, 3932; b) S. F. PEDERSEN, R. R. SCHROCK, M. R. CHURCHILL, H. J. WASSERMAN, *J. Am. Chem. Soc.* **1982**, *104*, 6808; c) R. R. SCHROCK, *Acc. Chem. Res.* **1986**, *19*, 342.
 - 9 For a pertinent example see ref. [8b].
 - 10 For leading references see: a) L. G. McCULLOUGH, R. R. SCHROCK, *J. Am. Chem. Soc.* **1984**, *106*, 4067; b) L. G. McCULLOUGH, R. R. SCHROCK, J. C. DEWAN, J. C. MURDZEK, *J. Am. Chem. Soc.* **1985**, *107*, 5987; c) I. A. WEINSTOCK, R. R. SCHROCK, W. M. DAVIS, *J. Am. Chem. Soc.* **1991**, *113*, 135; d) Y.-C. TSAI, P. L. DIACONESCU, C. C. CUMMINS, *Organometallics* **2000**, *19*, 5260; e) for an immobilized variant see: M. CHABANAS, A. BAUDOUIN, C. COPÉRET, J.-M. BASSET, *J. Am. Chem. Soc.* **2001**, *123*, 2062.
 - 11 a) R. R. SCHROCK, D. N. CLARK, J. SANCHO, J. H. WENGROVIUS, S. M. ROCKLAGE, S. F. PEDERSEN, *Organometallics* **1982**, *1*, 1645; b) J. H. FREUDENBERGER, R. R. SCHROCK, M. R. CHURCHILL, A. L. RHEINGOLD, J. W. ZILLER, *Organometallics* **1984**, *3*, 1563; c) M. L. LISTEMANN, R. R. SCHROCK, *Organometallics* **1985**, *4*, 74; d) J. SANCHO, R. R. SCHROCK, *J. Mol. Catal.* **1982**, *15*, 75.
 - 12 a) R. R. SCHROCK, *J. Chem. Soc., Dalton Trans.* **2001**, 2541; b) R. R. SCHROCK, *Chem. Rev.* **2002**, *102*, 145; c) H. FISCHER, P. HOFMANN, F. R. KREISSL, R. R. SCHROCK, U. SCHUBERT, K. WEISS (Eds.), *Carbyne Complexes*, VCH, Weinheim, **1988**.
 - 13 M. AKIYAMA, M. H. CHISHOLM, F. A. COTTON, M. W. EXTINE, D. A. HAITKO, D. LITTLE, P. E. FANWICK, *Inorg. Chem.* **1979**, *18*, 2266.
 - 14 a) Note that $(t\text{BuO})_3\text{W}\equiv\text{W}(\text{OtBu})_3$ is also able to effect alkyne metathesis, cf.: R. R. SCHROCK, M. L. LISTEMANN, L. G. STURGEON, *J. Am. Chem. Soc.* **1982**, *104*, 4291; b) for a computational study see: S. FANTACCI, N. RE, M. ROSI, A. SGAMELLOTTI, M. F. GUEST, P. SHERWOOD, C. FLORIANI, *J. Chem. Soc. Dalton Trans.* **1997**, 3845.
 - 15 R. R. SCHROCK, *Polyhedron* **1995**, *14*, 3177.
 - 16 M. A. STEVENSON, M. D. HOPKINS, *Organometallics* **1997**, *16*, 3572.
 - 17 a) J. A. K. DU PLESSIS, H. C. M. VOSLOO, *J. Mol. Catal.* **1991**, *65*, 51; b) H. C. M. VOSLOO, J. A. K. DU PLESSIS, *J. Mol. Catal. A: Chem.* **1998**, *133*, 205.
 - 18 D. VILLEMEN, P. CADIOT, *Tetrahedron Lett.* **1982**, *23*, 5139.
 - 19 a) N. KANETA, T. HIRAI, M. MORI, *Chem. Lett.* **1995**, 627; b) N. KANETA, K. HIKICHI, S. ASAKA, M. UEMURA, M. MORI, *Chem. Lett.* **1995**, 1055; c) M. NISHIDA, H. SHIGA, M. MORI, *J. Org. Chem.* **1998**, *63*, 8606.
 - 20 a) L. KLOPPENBURG, D. SONG, U. H. F. BUNZ, *J. Am. Chem. Soc.* **1998**, *120*, 7973; b) N. G. PSCHIRER, U. H. F. BUNZ, *Tetrahedron Lett.* **1999**, *40*, 2481.
 - 21 K. GRELA, J. IGNATOWSKA, *Org. Lett.* **2002**, *4*, 3747.
 - 22 G. BRIZIUS, U. H. F. BUNZ, *Org. Lett.* **2002**, *4*, 2829.
 - 23 D. VILLEMEN, M. HÉROUX, V. BLOT, *Tetrahedron Lett.* **2001**, *42*, 3701.
 - 24 A. FÜRSTNER, F. STELZER, A. RUMBO, H. KRAUSE, *Chem. Eur. J.* **2002**, *8*, 1856.
 - 25 Review: U. H. F. BUNZ, *Acc. Chem. Res.* **2001**, *34*, 998.
 - 26 See the following for leading references on applications of other alkyne metathesis catalysts to polymer synthesis: a) S. A. KROUSE, R. R. SCHROCK, *Macromolecules* **1989**, *22*, 2569; b) K. WEISS, A. MICHEL, E.-M. AUTH, U. H. F. BUNZ, T. MANGEL, K. MÜLLEN, *Angew. Chem.* **1997**, *109*, 522; *Angew. Chem. Int. Ed.* **1997**, *36*, 506–509; c) X.-P. ZHANG, G. C. BAZAN, *Macromolecules* **1994**, *27*, 4627.
 - 27 A. FÜRSTNER, C. MATHES, C. W. LEHMANN, *J. Am. Chem. Soc.* **1999**, *121*, 9453.
 - 28 Reviews: a) C. C. CUMMINS, *Chem. Comm.* **1998**, 1777; b) C. C. CUMMINS, *Prog. Inorg. Chem.* **1998**, *47*, 685.
 - 29 a) J. C. PETERS, A. L. ODOM, C. C. CUMMINS, *Chem. Comm.* **1997**, 1995;

- b) J. B. GRECO, J. C. PETERS, T. A. BAKER, W. M. DAVIS, C. C. CUMMINS, G. WU, *J. Am. Chem. Soc.* **2001**, 123, 5003; c) T. AGAPIE, P. L. DIACONESCU, C. C. CUMMINS, *J. Am. Chem. Soc.* **2002**, 124, 2412.
- 30 A. FÜRSTNER, C. MATHES, C. W. LEHMANN, *Chem. Eur. J.* **2001**, 7, 5299.
- 31 M. SATO, M. WATANABE, *Chem. Comm.* **2002**, 1574.
- 32 R. DEMBINSKI, S. SZAFERT, P. HAQUETTE, T. LIS, J. A. GLADYSZ, *Organometallics* **1999**, 18, 5438.
- 33 A. FÜRSTNER, C. MATHES, *Org. Lett.* **2001**, 3, 221.
- 34 A previous publication (J. H. FREUDENBERGER, R. R. SCHROCK, *Organometallics* **1986**, 5, 398) reports that tungsten alkylidyne complexes of this type are sufficiently nucleophilic to react with carbonyl compounds such as acetone, benzaldehyde, ethyl formate or even DMF. Although this seems to indicate a limited scope, complex **1** was found to be at least kinetically inert against these and many other electrophilic groups, cf. the examples in Sections 2.12.4.1–2.12.4.5 and Table 2.12-7.
- 35 A. FÜRSTNER, T. DIERKES, *Org. Lett.* **2000**, 2, 2463.
- 36 A. FÜRSTNER, K. GRELA, C. MATHES, C. W. LEHMANN, *J. Am. Chem. Soc.* **2000**, 122, 11799.
- 37 A. FÜRSTNER, G. SEIDEL, *Angew. Chem.* **1998**, 110, 1758; *Angew. Chem. Int. Ed.* **1998**, 37, 1734.
- 38 A. FÜRSTNER, O. GUTH, A. RUMBO, G. SEIDEL, *J. Am. Chem. Soc.* **1999**, 121, 11108.
- 39 For related cyclooligomerization reactions see: a) N. G. PSCHIRER, W. FU, R. D. ADAMS, U. H. F. BUNZ, *Chem. Comm.* **2000**, 87; b) P.-H. GE, W. FU, W. A. HERRMANN, E. HERDTWECK, C. CAMPANA, R. D. ADAMS, U. H. F. BUNZ, *Angew. Chem.* **2000**, 112, 3753; *Angew. Chem. Int. Ed.* **2000**, 39, 3607.
- 40 A. FÜRSTNER, G. SEIDEL, *J. Organomet. Chem.* **2000**, 606, 75.
- 41 A. FÜRSTNER, K. LANGEMANN, *Synthesis* **1997**, 792.
- 42 A. FÜRSTNER, A. RUMBO, *J. Org. Chem.* **2000**, 65, 2608.
- 43 W. P. D. GOLDRING, L. WEILER, *Org. Lett.* **1999**, 1, 1471.
- 44 B. AGUILERA, L. B. WOLF, P. NIECZYPOR, F. P. J. T. RUTJES, H. S. OVERKLEEF, J. C. M. VAN HEST, H. E. SCHOEMAKER, B. WANG, J. C. MOL, A. FÜRSTNER, M. OVERHAND, G. A. VAN DER MAREL, J. H. VAN BOOM, *J. Org. Chem.* **2001**, 66, 3584.
- 45 A. FÜRSTNER, O. GUTH, A. DÜFFELS, G. SEIDEL, M. LIEBL, B. GABOR, R. MYNOTT, *Chem. Eur. J.* **2001**, 7, 4811.
- 46 In this context, a recent publication of VILLEMIN et al. is noteworthy, cf. ref. [23].
- 47 a) A. FÜRSTNER, T. MÜLLER, *J. Am. Chem. Soc.* **1999**, 121, 7814; b) A. FÜRSTNER, T. MÜLLER, *J. Org. Chem.* **1998**, 63, 424; c) A. FÜRSTNER, F. JEANJEAN, P. RAZON, *Angew. Chem.* **2002**, 114, 2203; *Angew. Chem. Int. Ed.* **2002**, 41, 2097.
- 48 A. FÜRSTNER, K. RADKOWSKI, J. GRABOWSKI, C. WIRTZ, R. MYNOTT, *J. Org. Chem.* **2000**, 65, 8758.
- 49 A. FÜRSTNER, K. GRELA, *Angew. Chem.* **2000**, 112, 1292; *Angew. Chem. Int. Ed.* **2000**, 39, 1234.
- 50 Review: K. C. NICOLAOU, A. RITZÉN, K. NAMOTO, *Chem. Comm.* **2001**, 1523 and literature cited therein.
- 51 a) P. BERTINATO, E. J. SORENSSEN, D. MENG, S. J. DANISHEFSKY, *J. Org. Chem.* **1996**, 61, 8000; b) D. MENG, P. BERTINATO, A. BALOG, D.-S. SU, T. KAMENECKA, E. J. SORENSSEN, S. J. DANISHEFSKY, *J. Am. Chem. Soc.* **1997**, 119, 10073.
- 52 a) Z. YANG, Y. HE, D. VOURLOUMIS, H. VALLBERG, K. C. NICOLAOU, *Angew. Chem.* **1997**, 109, 170; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 166; b) K. C. NICOLAOU, Y. HE, D. VOURLOUMIS, H. VALLBERG, F. ROSCHANGAR, F. SARABIA, S. NINKOVIC, Z. YANG, J. I. TRUJILLO, *J. Am. Chem. Soc.* **1997**, 119, 7960.
- 53 a) D. SCHINZER, A. LIMBERG, A. BAUER, O. M. BÖHM, M. CORDES, *Angew. Chem.* **1997**, 109, 543; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 523; b) D. SCHINZER, A. BAUER, O. M.

- BÖHM, A. LIMBERG, M. CORDES, *Chem. Eur. J.* **1999**, 5, 2483.
- 54 A. FÜRSTNER, C. MATHES, K. GRELA, *Chem. Comm.* **2001**, 1057.
- 55 A. FÜRSTNER, K. RADKOWSKI, *Chem. Comm.* **2002**, 2182.
- 56 For a conceptually similar conversion of acyclic alkynes to (*E*)-alkenes see:
B. M. TROST, Z. T. BALL, T. JÖGE, *J. Am. Chem. Soc.* **2002**, 124, 7922.
- 57 A. FÜRSTNER, S. CASTANET, K. RADKOWSKI, C. W. LEHMANN, *J. Org. Chem.* **2003**, 68, 1521.
- 58 Note added in proof: For a facile synthesis of catalytically active molybdenum (VI) alkylidyne complexes from complex **2** and gem-dichlorides see: W. ZHANG, S. KRAFT, J. S. MOORE, *Chem. Commun.* **2003**, 832.
- 59 For a very recent example see: O. S. MILJANIC, K. P. C. VOLHARDT, G. D. WHITENER, *Synlett* **2003**, 29.

2.13

Metathesis of Silicon-Containing Olefins

Bogdan Marciniec and Cezary Pietraszuk

2.13.1

Introduction

While olefin metathesis has been extensively and successfully studied since the 1960s, reactions of this type were more widely applied to silicon-containing olefins only in the last decade of the 20th century, when well-defined Schrock- and Grubbs-type metal carbene complexes were used for catalysis (Figure 2.13-1) [1].

Substituted alkenylsilanes, particularly vinylsilanes and allylsilanes – products of cross-metathesis (CM), ring-closing metathesis (RCM), and tandem ring-opening metathesis/cross-metathesis (ROM/CM) – have been of significant importance to organic synthesis by opening the availability of suitable chemo-, regio- and stereo-selective routes [2, 3].

On the other hand, unsaturated organosilicon oligomers and polymers, particularly those having vinyl-silicon and allyl-silicon functionalities, have also found wide application as adhesives; membranes; materials of special electrophysical, optical, and thermal properties; and ceramics precursors [4–6]. The macromolecular organosilicon products can be synthesized by ADMET polymerization and copolymerization as well as by ROM polymerization.

In this chapter we present a short review of all synthetically and commercially valuable molecular and macromolecular unsaturated organosilicon compounds, with particular emphasis on vinyl- and allyl-substituted organosilicon derivatives. In this review the mechanistic considerations are limited to the novel processes occurring according to the mechanism different from that commonly accepted in the presence of well-defined Ru-, Mo-, and W-carbene complexes. Metathesis of alkenyl-substituted silicon compounds is included in the well-established general model of catalysis of metathesis. However, vinylsilicon compounds exhibit specific behavior in metathesis due to the strong steric and electronic influence of silicon on the double bond. According to our knowledge thus far, vinyl derivatives of organosilicon compounds, which are of fundamental industrial importance, are inert to productive homometathesis and ADMET polymerization in the presence of metallacarbene catalysts. These compounds undergo efficient condensation and polymerization, leading to metathesis-like products, formed according to the non-

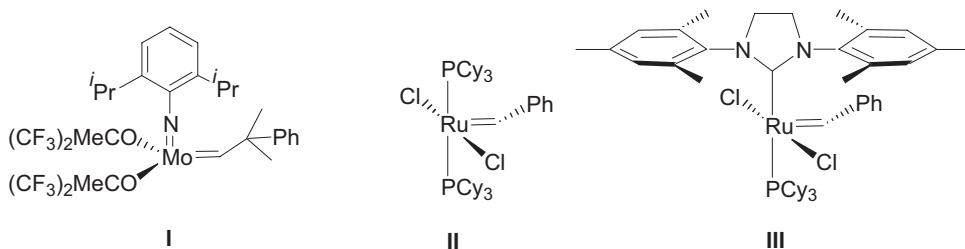


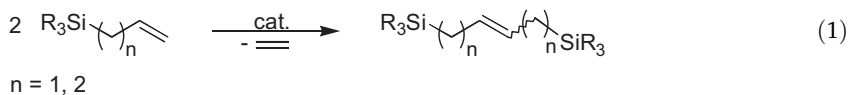
Fig. 2.13-1.

metallacarbene mechanism. Therefore, the synthetic routes and mechanistic aspects are also described for these processes [7].

2.13.2

Self-Metathesis of Alkenylsilanes

As we have already mentioned, although olefin metathesis has been extensively studied for the last 40 years, the information on metathesis of silicon-containing olefins is very scarce [1a]. A few examples of reactions proceeding in the presence of ill-defined catalysts according to Eq. (1) are summarized in [1a,f].

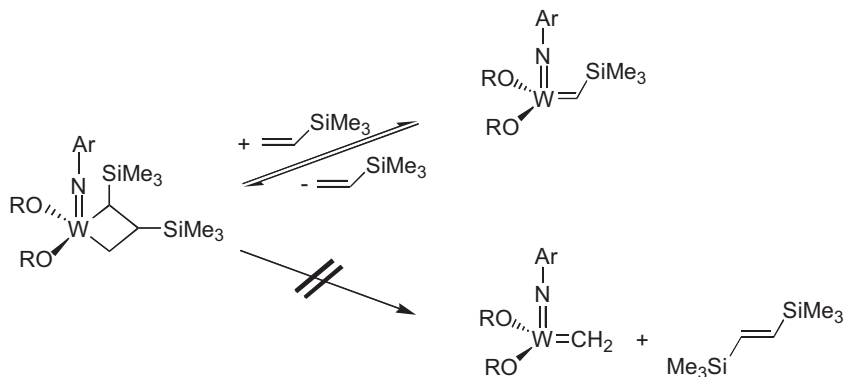


In a number of publications on metathesis of alkenylsilanes in the presence of well-defined Schrock- and Grubbs-type catalysts, the homometathesis of alkenylsilanes has been considered an undesirable side reaction. There is only one report on an effective self-metathesis of vinylsilanes. The ethylidene molybdenum complex $[\text{Mo}(\text{NO})_2(=\text{CHMe})(\text{OR})_2(\text{AlCl}_2)_2(\text{EtAlCl}_2)]$ (where $\text{R} = \text{Et}, \text{O}^i\text{Pr}$) has been reported to be an efficient catalyst for self-metathesis of vinyltrimethoxysilane [8]. However, no direct evidence has been given for a metallacarbene mechanism of this process. Inactivity of vinyl derivatives of organosilicon compounds to productive homometathesis is presumably due to the steric hindrance of silyl groups, which prevents the formation or productive decomposition of metallacyclobutanes containing two adjacent bulky silyl groups (Scheme 2.13-1) [9].

2.13.3

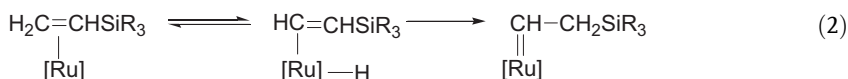
Cross-Metathesis vs. Silylative Coupling (*Trans*-Silylation) of Alkenes with Vinylsilanes

In 1984 the first example of very effective disproportionation (called “metathesis”) of vinyl-substituted silicon compounds, catalyzed by ruthenium (e.g., $[\text{RuCl}_2(\text{PPh}_3)_3]$ and $[\text{RuHCl}(\text{PPh}_3)_3]$) and rhodium (e.g., $\text{RhCl}_3/\text{LiAlH}_4$) com-



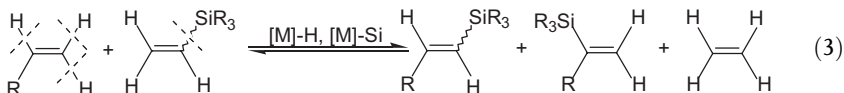
Scheme 2.13-1. Non-productive metathesis decomposition pathway of α,β -bis(silyl)-substituted tungstacyclobutane.

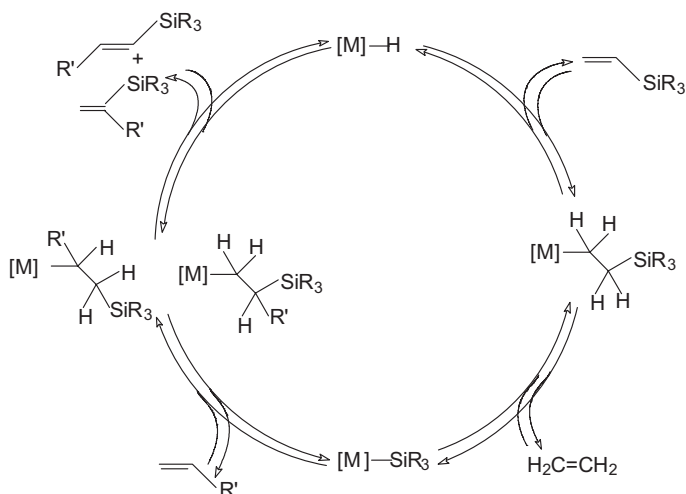
plexes, was reported [10]. This new synthetic route allowed preparation of a series of unsaturated silicon compounds in high yield (>70%) [10–13]. As follows from the experimental data as well as from the report by Seki et al. [14] on catalysis of “self-metathesis” (disproportionation) of vinylsilanes by $[\text{Ru}_3(\text{CO})_{12}]/\text{HSiPh}_3$ and $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$, the formation of a M–H bond could be a crucial step the initiation of catalytically active species in all the ruthenium (and rhodium) complexes as precursors of the catalyst. The activation of vinyl-substituted silicon compounds by precursor that initially does not contain a Ru–H bond was proposed to proceed as follows (Eq. (2)) [15]:



However, the experiments performed at that time with ill-defined catalysts did not distinguish between the reaction involving ruthenium carbene intermediates and/or the non-metallacarbene mechanism (described below).

Evidence for the migratory insertion of ethylene [16], vinylsilane [17], and styrene [18] into the Ru–Si bond yielding vinylsilane, two regioisomers (1,2- and 1,1-bis(silyl)ethene), and silylstyrene, respectively, revealed that in the reaction referred to as the “metathesis” of vinylsilanes and their “co-metathesis” with alkenes, instead of the C=C bond cleavage (formally characterizing alkene metathesis), a new type of olefin conversion occurred – silylative coupling of alkenes with vinylsilanes, also called dehydrogenative silylation, *trans*-silylation, or silyl group transfer (Eq. (3)) [7].



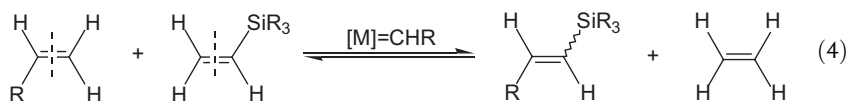


Scheme 2.13-2. Mechanism of silylative coupling of alkenes with vinylsilanes.

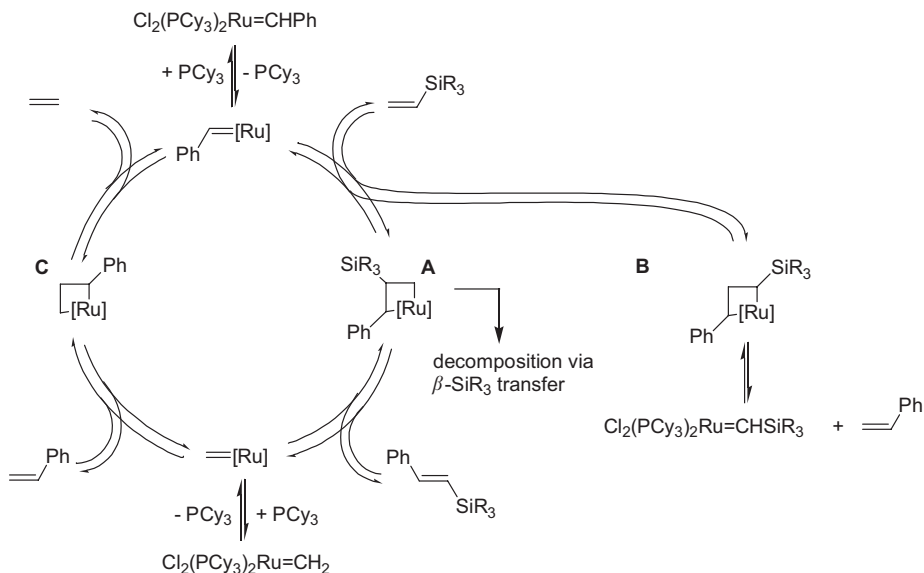
Subsequent synthetic and catalytic studies have shown that silylative coupling of alkenes with vinyl-substituted silicon compounds proceeds, similar to the hydrosilylation and dehydrogenative silylation reactions, via active intermediates containing M–Si (silicometallics) and M–H bonds (where M = Ru, Rh, Ir, Co, Fe). A mechanistic scheme of this new type of silyl olefin conversion involves the migratory insertion of alkene into the M–Si bond and vinylsilanes into the M–H bond, followed by β -H and β -Si elimination to give E-alkylsilyl ethene and ethene, respectively (see Scheme 2.13-2).

This mechanism of catalysis was proven by insertion of olefins into the M–Si bond [16–18] and insertion of vinylsilane into the M–H bond [16–20], by the stoichiometric reactions, and by mass spectrometric (MS) study of systems containing deuterium-labeled reagents [18, 19, 21, 22].

On the other hand, although well-defined or *in situ*-initiated metal-carbene complexes are inactive for self-metathesis of vinyl-substituted silanes and siloxanes, recent reports on high catalytic activity of molybdenum [23] and ruthenium [24–29] metallocarbene in cross-metathesis of vinyltrialkoxysilanes and vinyltrisiloxysilanes with alkenes and RCM of siladienes have opened new opportunities for applying metathesis in organosilicon chemistry. The reaction occurs under mild conditions, even at room temperature, according to Eq. (4):



Highly selective cross-metathesis of vinylsilanes and vinylsiloxanes with styrene proceeds according to the following catalytic cycle (Scheme 2.13-3):

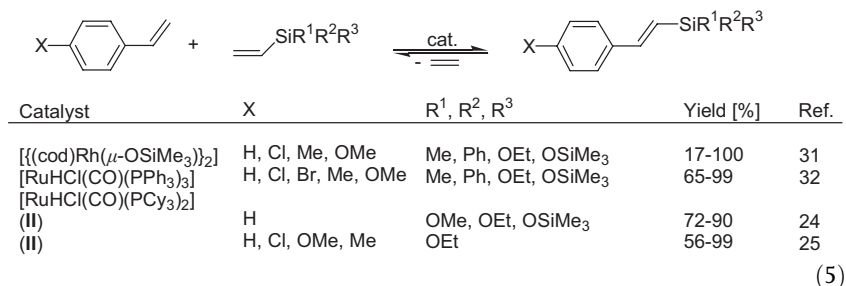


Scheme 2.13-3. Mechanism of vinylsilanes cross-metathesis with styrene.

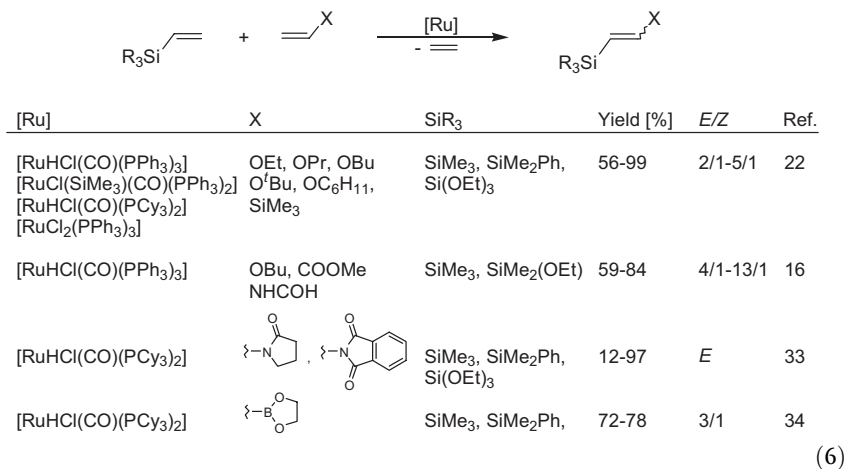
The catalysis is based on the commonly accepted mechanism in which ruthenium-methylidene and benzylidene complexes are the real catalysts. The mechanism was proposed on the basis of the studies of stoichiometric reactions including those with deuterium-labeled styrene [24, 30]. According to the mechanism, dissociation of PCy_3 from **II** generates the catalytically active species. Addition of vinylsilanes followed by oxidative cyclization gives either ruthenacycle **A** or **B**. Depending on the substituents at silicon, ruthenacycle **A** either collapses productively to give silylstyrene and methylidene complex ($\text{SiR}_3 = \text{Si}(\text{OMe})_3$, $\text{Si}(\text{OEt})_3$, $\text{Si}(\text{OSiMe}_3)_3$) or decomposes via β - SiR_3 transfer to metal, followed by reductive elimination (SiR_3 containing at least one methyl substituent) [30] and thus termination of the catalytic cycle.

Elimination of styrene from **B** yields the silylcarbene complex. However, only traces of styrene and no (silyl)carbene complex have been detected, suggesting that this pathway is either kinetically disfavored or highly reversible. The addition of styrene to methylidene complex, the formation of ruthenacycle **C**, and ethylene elimination complete the catalytic cycle. An analogous general mechanism for cross-metathesis of vinylsilanes with olefins has been proposed [25]. The mechanism clearly demonstrates why vinylsilanes active in cross-metathesis with a wide spectrum of olefins cannot be converted into bis(silyl)ethenes.

Efficient stereo- and regioselective synthesis of silylstyrenes was observed when styrene or *p*-substituted styrenes reacted with vinylsilanes in the presence of both ruthenium (or rhodium) complexes containing or generating M–H bond and Grubbs-type carbene complex (II). In all cases *E*-styrylsilanes and siloxanes were exclusively formed (Eq. (5)).



A series of 1-silyl-2-N(O or S)-substituted ethenes (with high preference for *E*-isomers) were synthesized via silylation of vinyl-substituted heteroorganic (N, O, S) compounds with vinylsilanes in the presence of ruthenium complexes containing or generating Ru–H and/or Ru–Si bonds (Eq. (6)). The reaction opens a general synthetic route for 1-silyl-2-heteroatom-substituted ethenes.



On the other hand, effective cross-metathesis of vinylsilanes with allyl-substituted heteroorganic compounds takes place in the presence of Grubbs catalyst. Under optimum conditions, the reaction yields 1-silyl-3-N(O or S)-substituted propenes with moderate to high yield (Eq. (7)):



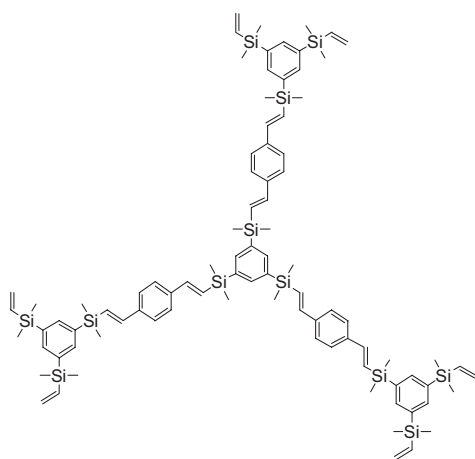
Y		SiR ₃	Yield [%]	E/Z	Ref.
SiR ₃	SiMe ₃ , Si(OEt) ₃	Si(OEt) ₃	71, 95	E, 15/1	25
OR	OEt, OBU, OC ₆ H ₁₁ , OPh, OCH ₂ Ph, OSiMe ₃ , glycidyloxy,	Si(OMe) ₃ , Si(OEt) ₃ , Si(OSiMe ₃) ₃	50-95	5/1-12/1	26
OCOR	OCOMe, OCOEt, OCOPr	Si(OEt) ₃	87-89	4/1-14/1	27
NR ₂	NMePh, N(COMe)Ph	Si(OEt) ₃	57, 63	6/1, traces Z	33
SR	SCMe ₃	Si(OEt) ₃	57	3/1	33

(7)

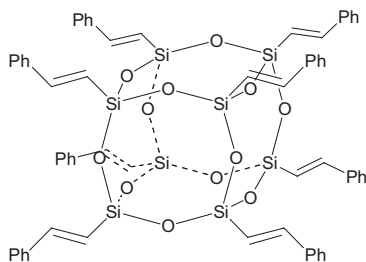
In view of recent reports, it seems appropriate to use the reaction of *trans*-silylation for synthesis of other types of unsaturated compounds, particularly for the synthesis of novel organosilicon starburst compounds having a silicon-bridged, π -conjugated structure, which is expected to have potential optoelectronic properties. The effective functionalization of 1,3,5-trivinylbenzene by the respective reactions with 1,4-divinylbenzene leads to the formation of G(1) dendrimers (Figure 2.13-2a) [35].

Organo-substituted octasilsesquioxane has been prepared by cross-metathesis of vinylsilsesquioxane with olefins in the presence of I [23]. Similar products were obtained via silylative coupling in the presence of Ru–H (Ru–Si) complexes and the cross-metathesis catalyzed by ruthenium-carbene complex II. For octasteryl-silsesquioxane (Figure 2.13-2b) crystallographic structure has been solved [36].

The reactions of vinylcyclosiloxanes and vinylcyclosilazanes with styrene gave products in the presence of [RuHCl(CO)(PCy₃)₂] and opened a new route for



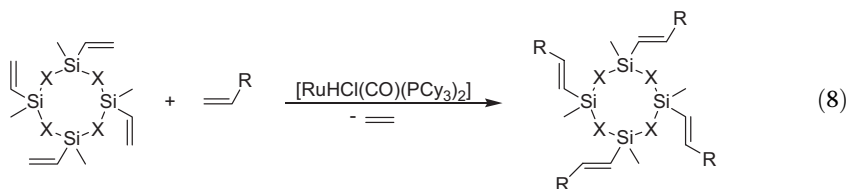
a)



b)

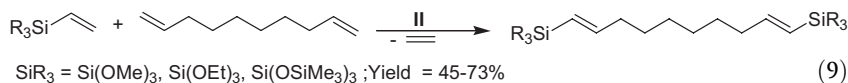
Fig. 2.13-2.

functionalized monomers to ring-opening polymerization of cyclosiloxanes and cyclosilazanes (Eq. (8)) [37].



X = O, NH; R = Ph; Yield = 83-95 %; only E

Cross-metathesis of 1,9-decadiene with an excess of trialkoxy- and trisiloxy-substituted vinylsilanes results in the formation of *E,E*-1,10-bis(silyl)-1,9-decadienes (Eq. (9)) [29].



SiR₃ = Si(OMe)₃, Si(OEt)₃, Si(OSiMe₃)₃; Yield = 45-73%

2.13.4

Cross-Metathesis of Allylsilanes with Alkenes

Allyltrimethylsilane has been demonstrated to be effectively transformed via cross-metathesis with a variety of unsaturated organic derivatives. Different types of homogeneous, heterogeneous classical, and well-defined catalyst/catalytic systems have been proved active for the reaction. Early examples of the reaction occurring in the presence of ill-defined catalysts have been reviewed [1a,f]. Crowe has demonstrated the effective cross-metathesis of allyltrimethylsilane with a series of alkenes [38, 39] catalyzed by I (Eq. (10)).

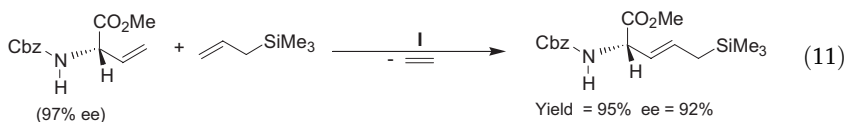


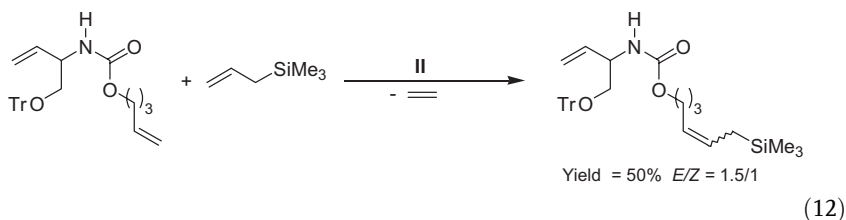
R = Ph, CN, (CH₂)₃Ph, (CH₂)₃Br, (CH₂)₃OBr, (CH₂)₃OSiBu₃, (CH₂)₃CN, etc.

Yield of 1 = 34-92%; *E/Z* = 2.6/1-4.9/1, *E* (for R = Ph), 1/4.7 (for R = CN);

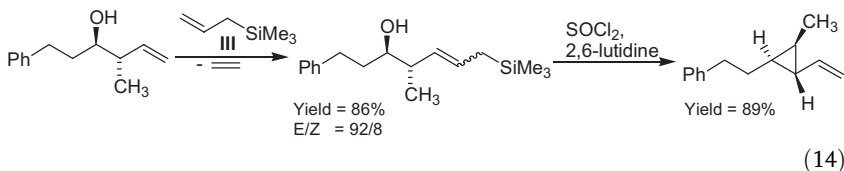
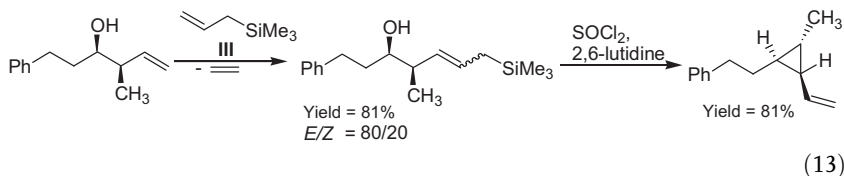
Yield of 2 = 0-26%;

Ruthenium-catalyzed cross-metathesis of allyltrimethylsilane with allylbenzene leads to a mixture of *E* and *Z* products [40]. Cross-metathesis of allylsilanes with α,β -unsaturated carbonyl compounds results in the formation of functionalized allylsilanes with high *E/Z* ratios [41]. Cross-metatheses of allyltrimethylsilane with olefins do not degrade the optical purity of chiral olefins (Eq. (11)) and can be performed chemoselectively (Eq. (12)) [42].

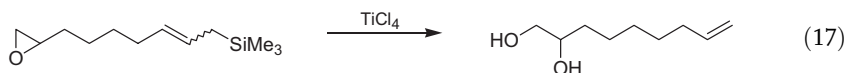
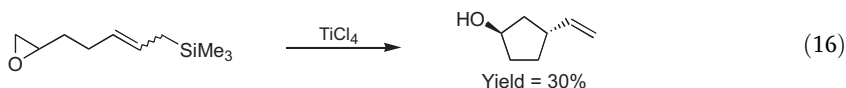
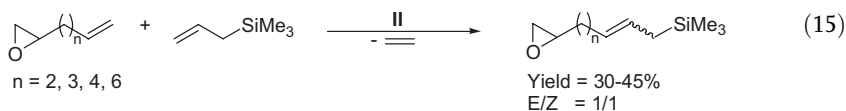




Cross-metathesis has been successfully applied to carbohydrate derivatives. *O*-allyl- α -*D*-galactopyranoside was effectively reacted with allyltrimethylsilane [43, 44]. Cross-metathesis of allyltrimethylsilane with homoallylic alcohols containing both *anti*- (Eq. (13)) and *syn*-allylic (Eq. (14)) substituents was reported to proceed effectively and display enhanced *E*-selectivity [45, 46]. The reaction was a key step in the synthetic route leading to vinylcyclopropanes.



The effective reaction of allyltrimethylsilane with alkenylepoxides in the presence of **II** leads to products (Eq. (15)) that represent potentially useful synthetic building blocks for Lewis acid-mediated cyclization and condensation reactions (Eqs. (16) and (17)) [47].



Cross-metathesis of allylsilane with terminally unsaturated α -hydroxy and α -ketoferrocenes has been also reported [48]. Polymer-supported synthesis with

an allylsilyl unit as a linker is another field of application of alkenylsilanes. Divinylbenzene cross-linked allyldimethylsilylpolystyrene was reported to undergo a highly efficient ruthenium-catalyzed cross-metathesis with functionalized terminal alkenes (Eq. (18)) [49].



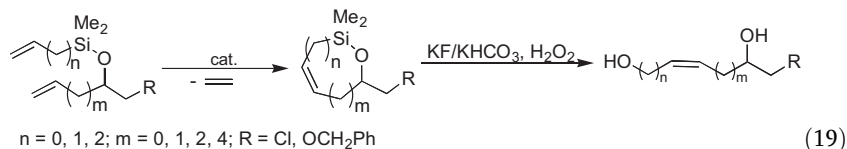
Products of the cleavage were liberated by protodesilylation with TFA under mild conditions.

2.13.5

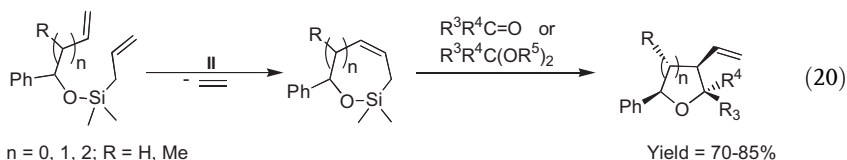
Ring-Closing Metathesis of Silicon-Containing Dienes

Some earlier examples of RCM involving the $\text{H}_2\text{C}=\text{CHSi}$ moiety have been recently reviewed [1a,f, 50, 51]. For the reactions performed in the presence of ill-defined catalyst systems, see [52–57]. The dynamic development of RCM and its applications to organic synthesis have brought about a growing interest in RCM of silicon-containing dienes. A number of valuable organic applications have been proposed over the last few years. From the point of view of RCM applications, as follows from available data, the most important are the silicon-tethered processes.

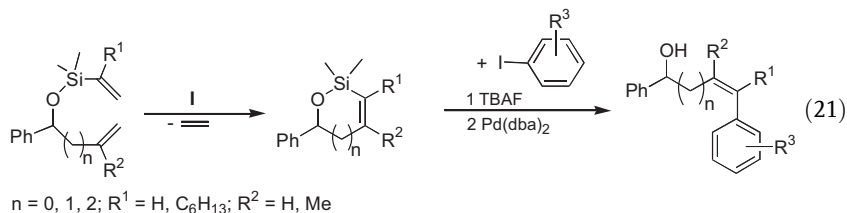
Grubbs has reported a synthetic strategy leading to highly functionalized organic molecules that involved RCM of silicon-tethered unsaturated organic fragments and oxidative cleavage of the cycles formed. Acyclic silyl ether dienes, easily available via silylation of secondary alcohols in the presence of molybdenum (I), ruthenium vinylcarbene $[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(\text{=CHCH}=\text{CPh}_2)]$, and ruthenium benzylidene (II) complexes, gave RCM products [58]. Obtained 6–8- and 10-membered rings underwent the oxidative cleavage to give hydroxy alkenes (Eq. (19)) [58].



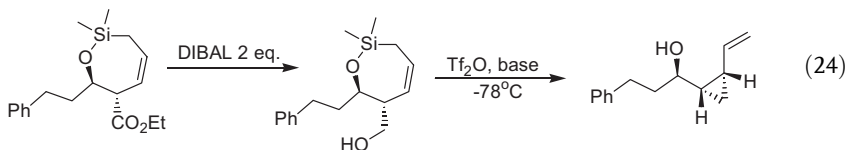
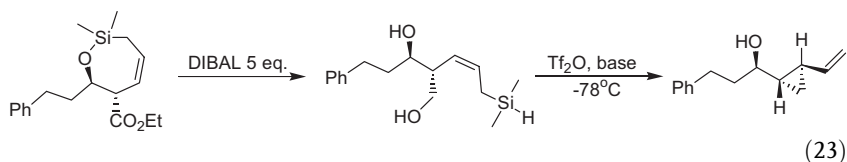
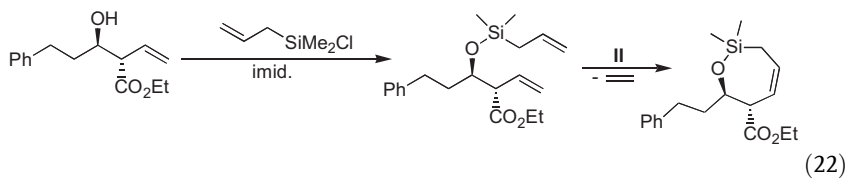
A series of substituted tetrahydrofurans and tetrahydropyrans were synthesized via RCM of silyl ether dienes followed by a modified Sakurai reaction (Eq. (20)) [59].



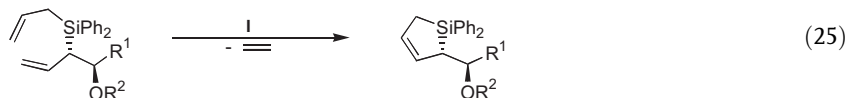
A similar method was reported by Cassidy [60]. In the method developed by Denmark, effective ring-closing metathesis of a series of vinylsilyl alkenyl ethers in the presence of **I** was followed by palladium-catalyzed cross-coupling with aryl iodides (Eq. (21)) [61].



A practical and efficient route for the stereoselective conversion of homoallylic alcohols to diastereomerically pure substituted cyclopropanes was developed by Taylor (Eqs. (22–24)) [46]. The strategy involves RCM of substituted silyl ether dienes (Eq. (22)).

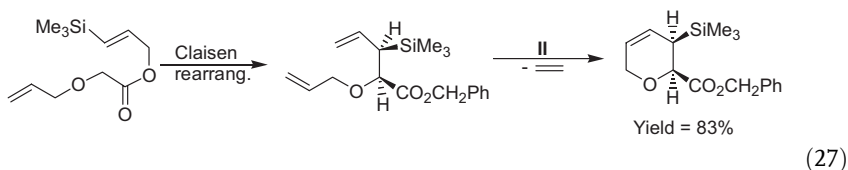
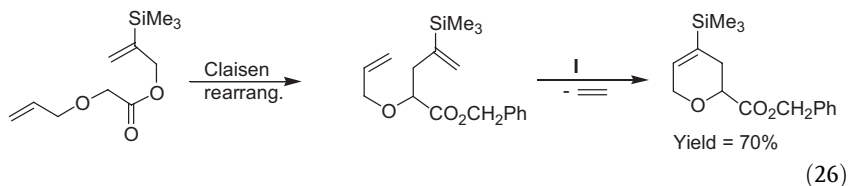


Regio- and stereoselective syntheses of C-2-functionalized silacyclopent-3-enes have been developed via RCM of the appropriate diallylsilanes (Eq. (25)) [62].

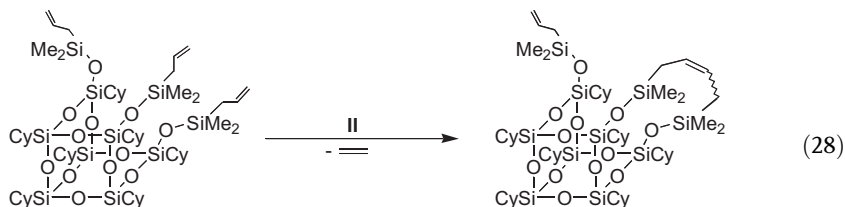


Silaketals constitute another group of convenient starting materials for silicon-tethered syntheses involving RCM [63–68]. However, these processes are beyond the scope of this review. Unsaturated rings of different sizes containing silicon atoms were synthesized via RCM of different silicon-containing dienes [69–75].

Stereoselective synthesis of functionalized carbocyclic and heterocyclic compounds via tandem ester enolate Claisen rearrangement/RCM was reported by Piscopio (Eqs. (26) and (27)) [76]. At the same time, a similar method was proposed by Burke [77].



Synthesis of an analogous series of trimethyl-substituted carbo- and heterocycles via RCM in the presence of **III** has been recently reported by Gouverneur [78]. A series of novel, alkenylidene-bridged silsesquioxanes has been synthesized via RCM (Eq. (28)) [79]. The molecules obtained are interesting building blocks for new materials or a platform for macrocyclic hosts.



Application of chiral Mo-based complexes, especially those containing substituted biphen- or binol-derived ligands (Figure 2.13-3), to the kinetic resolution of chiral dienes by asymmetric ring-closing metathesis (ARCM) has been recently reviewed [80].

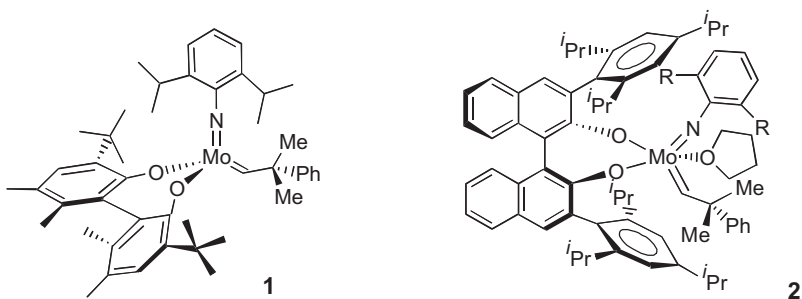
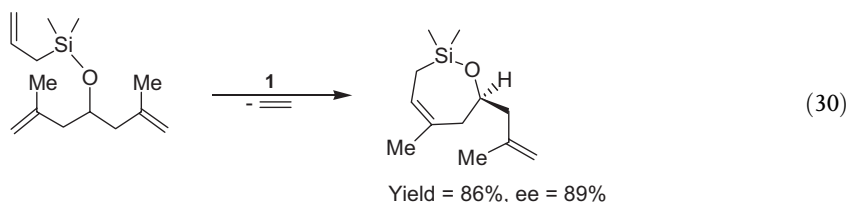
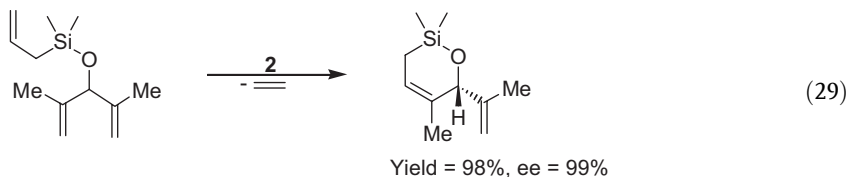
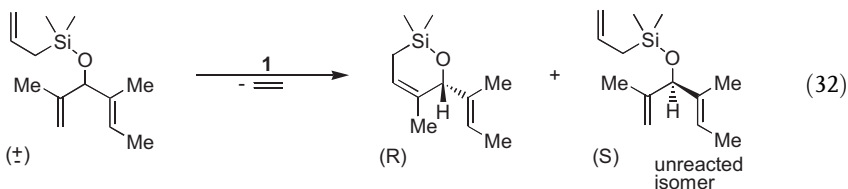
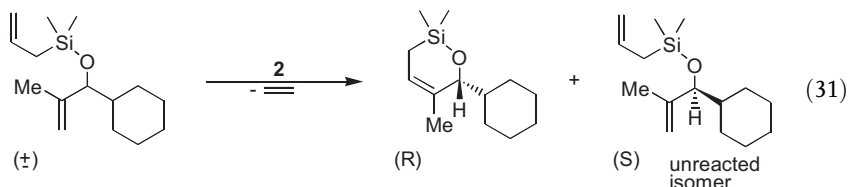


Fig. 2.13-3.

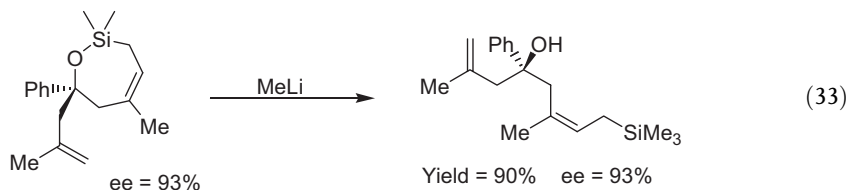
A number of examples of enantioselective cyclization of silicon-containing trienes and tetraenes have been reported. The reactions lead to the formation of 6- or 7-membered rings with very high yield and enantiomeric excess (*ee*) (Eqs. (29) and (30)). For other examples, see [80–87].



Desymmetrization of prochiral trienes seems to be the most significant application of this methodology; however, very effective kinetic resolutions were described for a number of monomeric acyclic dienes (Eqs. (31) and (32)). For more examples, see [80, 81, 84].



The non-racemic chiral, medium-ring silanes obtained are versatile compounds that can be employed to prepare numerous tertiary alcohols. A representative example is depicted in Eq. (33) [82].

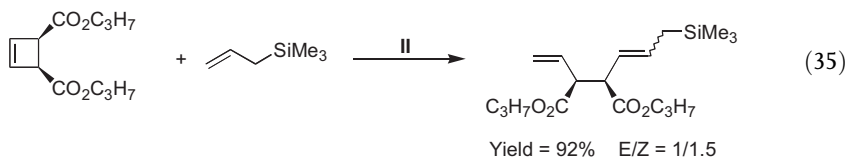
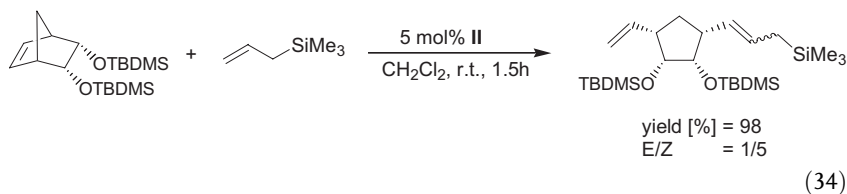


2.13.6

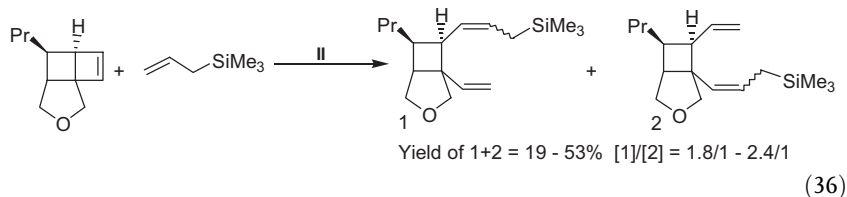
Ring-Opening Metathesis/Cross-Metathesis

For a single example of ROM/CM involving alkenylsilanes in the presence of the ill-defined homogeneous catalyst WCl_6 /1,1,3,3-tetramethyl-1,3-disilacyclobutane see reference [88].

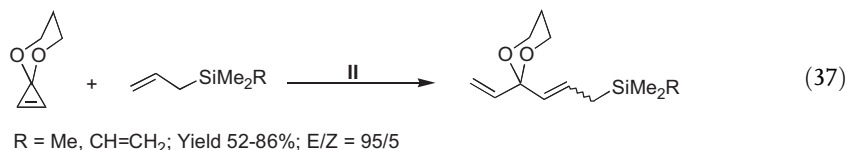
Selective ROM/CM of strained alkenes (norbornene derivatives, cyclooctene, and substituted cyclobutenes) with allyltrimethylsilane was reported by Blechert (Eqs. (34) and (35)) [89]. ROM/CM, especially with cyclooctene and cyclobutene derivatives, provides an exciting route to unsymmetric acyclic dialkenes.



The allylsilane reaction with tricyclic cyclobutenes was studied by Snapper (Eq. (36)) [90].

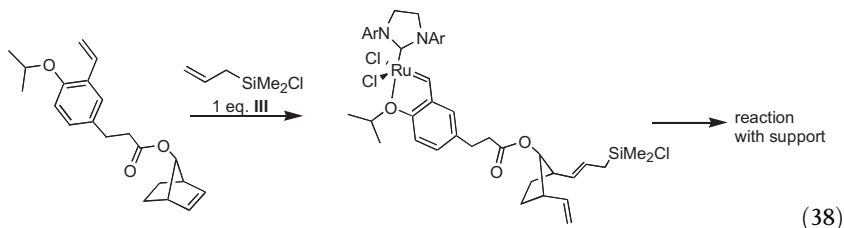


Grubbs complex **II** efficiently catalyzes ring-opening cross metathesis of cyclopropanone ketal with terminal alkenes to afford 1,4-divinyl ketone ketals in good yields (Eq. (37)) [91]. Mono- and diallyl-substituted silanes are efficiently transformed in the reaction.

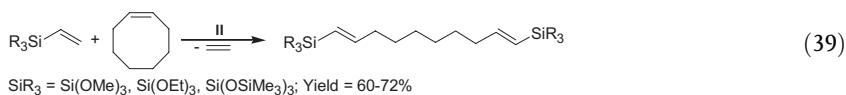


ROM/CM has been applied in the method for growing covalently attached polymer onto crystalline Si(111) surfaces [92], and an efficient strategy for surface functionalization of monolytic sol-gels has been reported (Eq. (38)) [93]. The

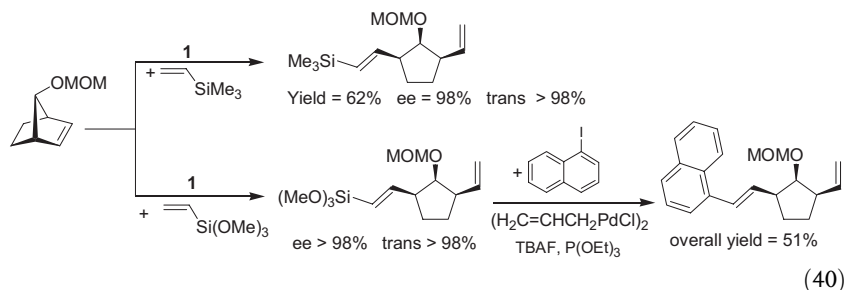
reaction with allylchlorodimethylsilanes was used for functionalization of organic molecules to make possible the bonding of ruthenium-carbene complex with inorganic support bearing a silanol groups on its surface.



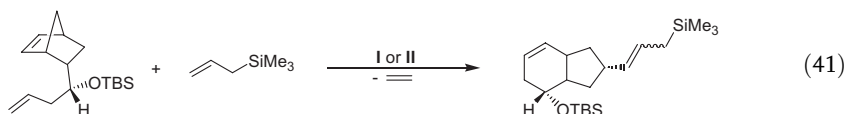
Cross-metathesis of cyclooctene with trialkoxy- and trisiloxy-substituted vinylsilanes leads under optimum conditions to the formation of *E,E*-1,10-bis(silyl)-1,9-decadienes (Eq. (39)) [29].



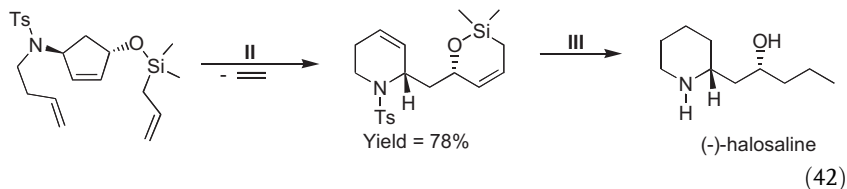
ROM/CM of substituted norbornene with $\text{CH}_2=\text{CHSiMe}_3$ and $\text{CH}_2=\text{CHSi}(\text{OMe})_3$ in the presence of a chiral molybdenum complex (1) (Figure 2.13-3) has been reported (Eq. (40)) [94, 95]. The method, in general, offers a valuable catalytic approach to optically pure materials. An example of application of a trimethoxysilyl derivative to Pd-catalyzed cross-coupling, leading to optically pure cyclopentyl dienes, has been proposed (Eq. (40)) [94, 95]. Achievements in AROM/CM to date are summarized in [94].



Blechert has described synthesis of [n.3.0] bicyclic derivatives with different ring sizes and functional groups in a single domino process [96]. In an excess of allyltrimethylsilane, bicyclic product was obtained in high yield (Eq. (41)).



Formally, the reaction combines the ring opening of norbornene, ring-closing metathesis with terminal double bond, and cross-metathesis with a second alkene. In another example, the domino metathesis involving an allylsilyl derivative was applied as a step in the synthesis of (–)-halosaline (Eq. (42)) [97].

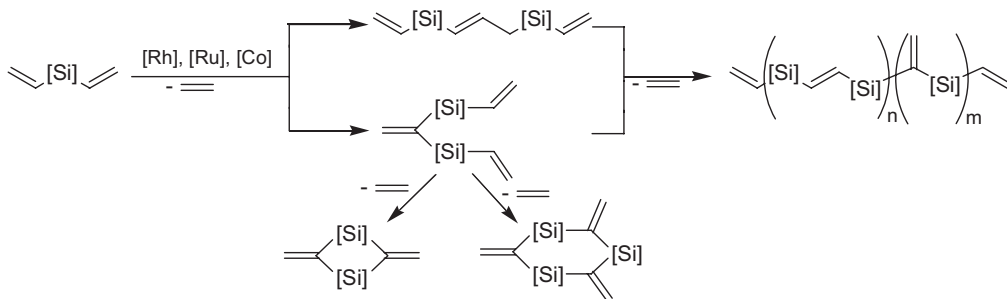


2.13.7

Polycondensation vs. Ring Closing of Divinyl-Substituted Silicon Compounds

Polymers possessing regularly alternative carbon/silicon or heteroatom/silicon (carbosilane, siloxane, silazane) linkages within the main chain, such as poly(silylene-alkenylene)s and poly(silylene-vinylene-arylene)s, etc., are of particular interest since the introduction of organic segments generally increases thermal stability and can improve mechanical properties of subsequent elastomers without sacrificing advantages of organosilicon polymers. Linear polycarbosilanes are an important class of silicon-containing polymers because of their thermal, electronic, and optical properties [4–6]. They are also precursors for ceramic materials.

Divinyl silicon derivatives, similar to monovinylsubstituted silicon compounds, are completely inert to productive homometathesis, in particular acyclic diene metathesis (ADMET) polymerization. However, it has been shown in earlier reports that in the presence of ruthenium, rhodium, and cobalt complexes containing or generating M–H, and/or M–Si bonds, divinyl-substituted silicon compounds undergo de-ethenated (poly)condensation to yield a mixture of linear oligomers and cyclic unsaturated siloxanes, silazanes, and carbosilanes (Scheme 2.13-4) [7].

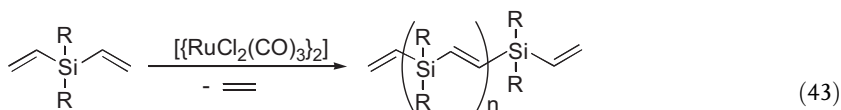


[Si] = SiMe₂, SiMe₂CH₂SiMe₂, SiMe₂NHSiMe₂, SiMe₂OSiMe₂

Scheme 2.13-4. Polycondensation vs. ring closing of divinyl-substituted silicon compounds.

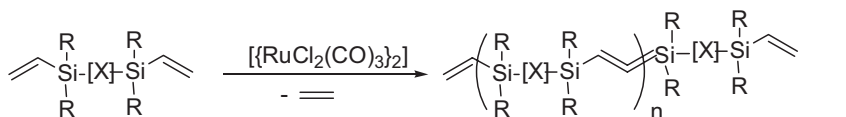
Mechanistic pathways for the condensation of divinylsilicon compounds are similar to well-established ones for monovinylsilanes to yield in the first step two isomeric *trans*- and *gem*-bis(vinylsilyl)ethenes, respectively.

Polycondensation of divinyltrimethylsilane, divinyltetramethyldisiloxane, and divinyltetramethyldisilazane carried out in the presence of $[\text{RuCl}_2(\text{PPh}_3)_2]$ or $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$ gives silylene-vinylene ($M_n = 1510$, PDI = 1.19) [98], siloxylene-vinylene ($M_n = 1815$; PDI = 1.16) [99], and silazanylene-vinylene ($M_w = 2380$, PDI = 1.21) [100] oligomers. However, under optimum conditions (in the presence of $[\{\text{RuCl}_2(\text{CO})_3\}_2]$) *trans*-tactic polysilylene-vinylenes (Eq. (43)) [101], polysiloxylene-vinylene [101], polysilazanylene-vinylenes [100], and polyalkylene-silylene-vinylenes (Eq. (44)) [102] can be synthesized:



R = Me; $M_w = 8200$; PDI = 1.32

R = Ph; $M_w = 3800$; PDI = 1.50



[X] = O; R = Me; $M_w = 8500$; PDI = 1.50

O; R = OEt; $M_w = 4900$; PDI = 1.58

NH; R = Me; $M_w = 813$;

$(\text{CH}_2)_n$; R = Me; $n = 0-4$; $M_w = 5500-9500$; PDI = 1.18-1.61

In the presence of rhodium complexes, divinyltetramethyldisiloxane, divinyltetramethyldisilazane, and divinyltrimethylsilane undergo condensation predominantly to dimeric and trimeric *gem*-products followed by their ring closure to yield a respective cyclocarbosiloxane [103, 104], cyclocarbosilazane [105], and cyclocarbosilane [105] with exocyclic methylenes (Figure 2.13-4).

Synthesis of cyclocarbosilanes containing one exocyclic methylene via ruthenium-catalyzed intermolecular ring closure of bis(vinyltrimethylsilyl)ethane and bis(vinyltrimethylsilyl)butane was reported by Wakatsuki [106].

It is worth emphasizing that contrary to the ring-closing diene metathesis, which recently has become a very common method for preparation of endocyclic organic

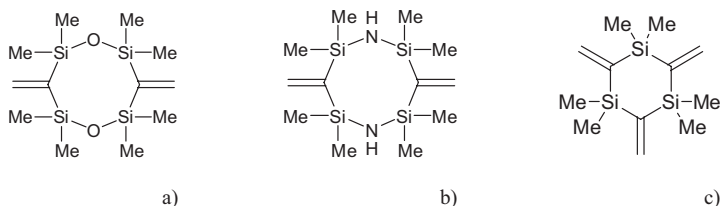
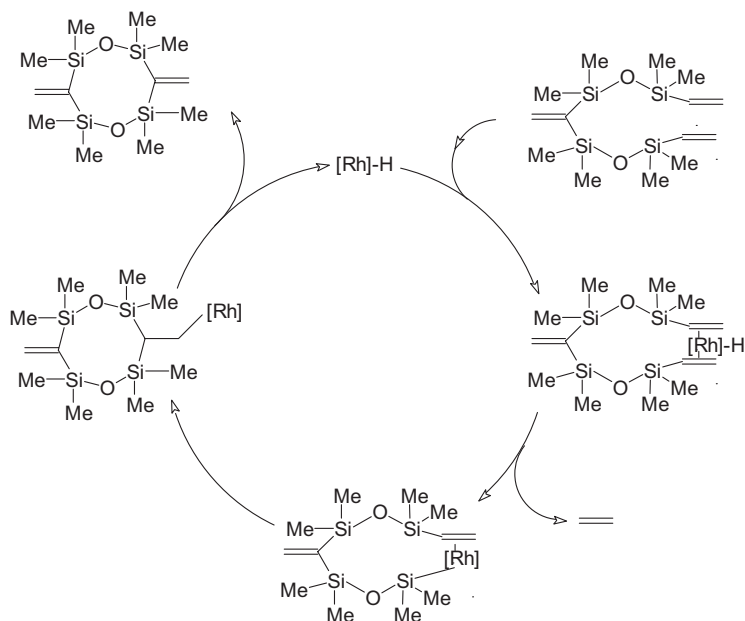


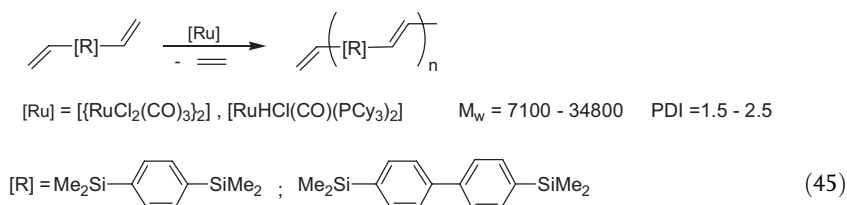
Fig. 2.13-4.

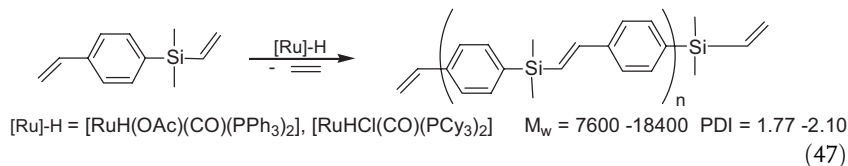
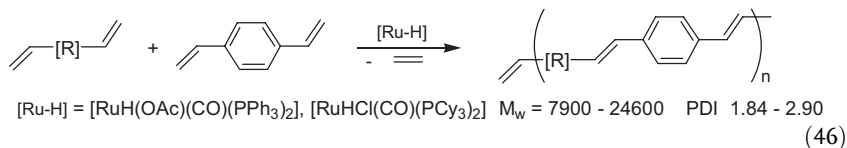
(and heteroorganic) unsaturated compounds, the above-mentioned ring closure opens an original route to the preparation of organosilicon compounds containing exocyclic methylenes. The following catalytic scheme describing the formation of such cycles from dimeric *gem* isomers, proceeding preferably in the presence of rhodium complexes, can be proposed (for divinyltetramethyldisiloxane) (Scheme 2.13-5) [103]:



Scheme 2.13-5. Mechanism of ring-closure of *gem*-bis(vinylsiloxy)ethenes catalyzed by Rh-H complex.

Poly-*p*-phenylene-vinylene-based polymers containing a silicon atom in the main chain are of great interest because of their efficient photoluminescence and potentially useful electroluminescence properties [107]. They are expected to find application as blue light-emitting polymeric materials. The introduction of silicon atoms into π -conjugated systems seems to affect the LUMO of the π -conjugated system and improves solubility and processability due to increased chain flexibility. The silylative-coupling (SC) polycondensation procedure has been effectively used to synthesize various poly(arylene-silylene-vinylene)s (Eqs. (45–47)) [108–110]:

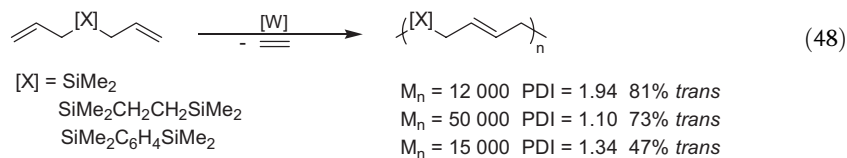




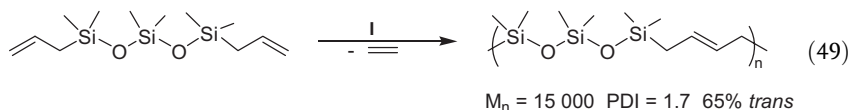
2.13.8

ADMET Polymerization of Silicon-Containing Dienes

ADMET oligo- and polymerization of dienes containing silicon in the main chain are convenient methods of polycarbosilanes preparation. Early examples of ADMET of diallyl- and higher dialkenyl-substituted silanes have been the subject of several reviews [1a, 50, 51, 111]. For a recent review, see [112]. Methylene spacer unit(s) between the double bond and the silicon are necessary in order to effectively polymerize silicon-containing dienes. Diallyldimethylsilane, bis(allyldimethylsilyl)ethane, and bis(allyldimethylsilyl)benzene have been successfully polymerized in the presence of the Schrock-type tungsten alkenylidene catalyst $[(\text{CF}_3)_2\text{MeCO}]_2(\text{NAr})\text{W}(=\text{CHR})$ (where $\text{R} = \text{tBu}$ or CMe_2Ph ; $\text{Ar} = 2,5\text{-diisopropylphenyl}$) (Eq. (48)) [113].



High average *trans* content obtained is typical of ADMET chemistry. A series of siloxane unit-containing dienes has been polymerized via ADMET (Eq. (49)) [114].



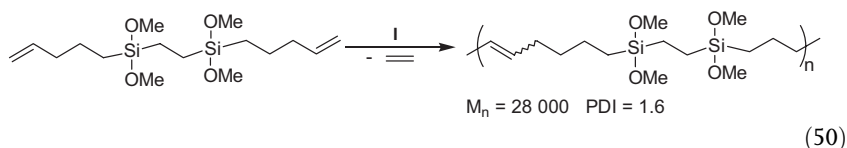
Low glass transition temperatures and high thermal stability have been observed for the poly(carbosiloxanes) obtained, which is expected of polymers containing siloxane linkages. Organofunctionalized polysiloxanes show a valuable combination of properties such as thermal stability, low temperature flexibility, and hydrophobicity.

A copolymer of high structural regularity was obtained via ADMET co-

polymerization of α,ω -telechelic carbosiloxane macromonomers with a rigid small aromatic molecule of 4,4'-di-*trans*-1-propenylbiphenyl in the presence of $[(\text{CF}_3)_2\text{MeCO}]_2(\text{NAr})\text{W}(=\text{CHCMe}_2\text{Ph})$ (where Ar = 2,5-diisopropylphenyl). The copolymer obtained underwent light-initiated cross-linking under an inert atmosphere and degraded after a prolonged exposure to air under ambient conditions [115].

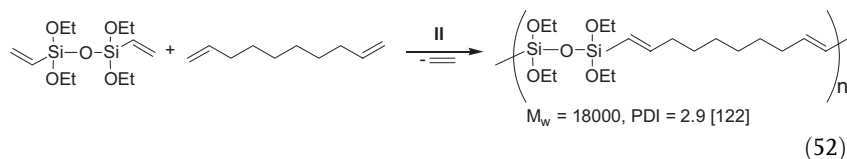
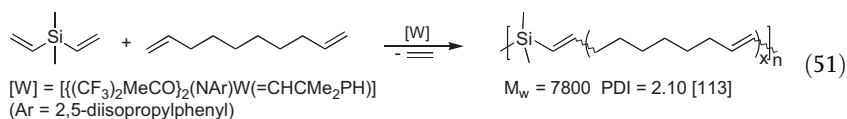
Poly(chlorocarbo)silanes have been obtained via ADMET polymerization of dialkenylchloromethylsilane and dialkenyldichlorosilane in the presence of **I** [116–119]. These chlorofunctionalized silanes offer the opportunity of producing materials having a broad range of properties, as the chloro substituent can be easily exchanged [120].

Dialkenylcarbosilanes containing methoxysubstituents at silicon have been polymerized by ADMET in the presence of **I** (Eq. (50)) [121].

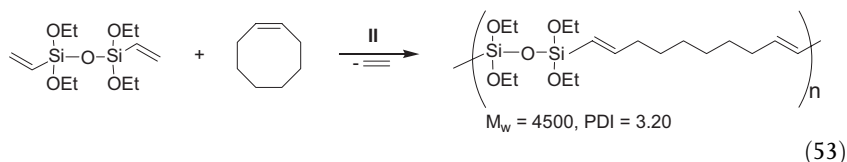


Copolymerization of the above-mentioned monomer with dialkenyltetramethylidisiloxane produces a linear thermoplastic material. The polymers can be subsequently triggered with water to generate cross-links [121].

Vinylsilanes, which were inactive in ADMET homopolymerization, undergo copolymerization with 1,9-decadiene (Eqs. (51) and (52)). On the basis of NMR data, no evidence for the consecutive vinylsilane linkages has been found.



An analogous polymer was obtained when cyclooctene was used instead of diene (Eq. (53)) [29].



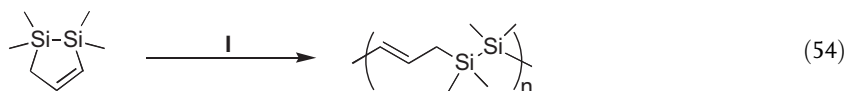
2.13.9

Ring-Opening Metathesis Polymerization of Silacycloalkenes

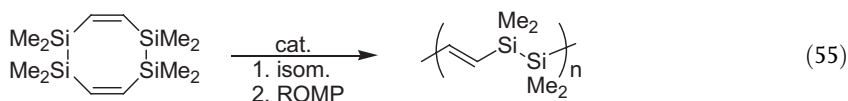
This reaction is a convenient method of the synthesis of unsaturated polymers containing silicon atom in the main polymer chain.

1,1-Disubstituted-1-silacyclopent-3-enes have been successfully polymerized via ROMP in the presence of different catalytic systems [56, 69, 123, 124]. However, a similar polymer can be also obtained by anionic polymerization of the same monomer [124, 125].

1,1,2,2-tetramethyl-1,2-disilacyclopent-3-ene was polymerized in the presence of **I** [126]. Polymerization proceeded both stereo- and regioselectively. Exclusive formation of head-to-tail polymer with 97% of *trans* geometry was observed (Eq. (54)).



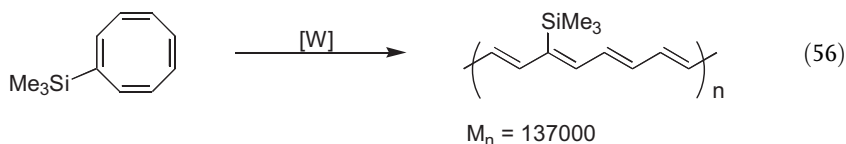
The tetrasilane analogue of cyclooctadiene was polymerized in the presence of W- and Mo-based Schrock-type catalysts to give soluble disilylenevinylene polymer with hybrid σ - π conjugation (Eq. (55)) [127].



2.13.10

Ring-Opening Metathesis Polymerization of Silyl-Substituted Cycloalkenes

A number of reviews on polymerization of organosilicon cycloalkenes have been published [1, 51, 111]. Ring-opening metathesis polymerization of silyl-substituted cycloalkenes is a convenient method for the synthesis of silyl-substituted polymers and co-polymers. 1-(Trimethylsilyl)cyclobutene was polymerized in the presence of Cassey carbene complex $[(\text{CO})_5\text{W}=\text{CPh}_2]$ [122]. The reaction provided a high yield of the polymer, which showed perfect head-to-tail structure and 100% *cis* configuration of double bonds. Grubbs et al. conducted the polymerization of trimethylsilylcyclooctatetraene in the presence of the Schrock-type tungsten alkylidene complex $[\{(\text{CF}_3)_2\text{MeCO}\}_2(\text{NAr})\text{W}(=\text{CHR})]$ ($\text{R} = t\text{-Bu}$; $\text{Ar} = 2,6\text{-diisopropylphenyl}$) (Eq. (56)) [129, 130].



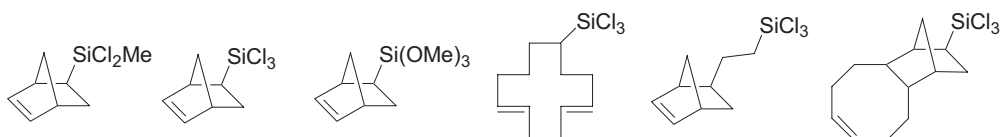


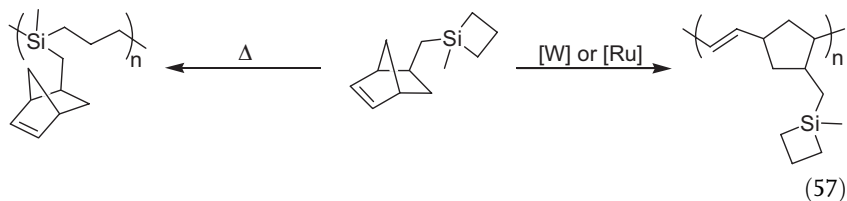
Fig. 2.13-5.

Thermal isomerization or flash photolysis was used to obtain *trans* geometry of the carbon-carbon double bond, which showed enhanced conjugation and conductivity. This polymer has a number of possible applications due to its solubility and conductivity. For instance, I_2 -doped poly(trimethylsilylcyclooctatetraene) can be used in Schottky barrier-type solar cells [131].

The majority of the literature deals with silyl-substituted norbornenes and their polymerization [51, 111, 132–136]. 2-(Trimethylsilyl)norbornadiene also was successfully polymerized via ROMP in the presence of a $WCl_6/SnMe_4$ system [137]. The introduction of $SiMe_3$ and related siloxyl groups into poly(cyclopentenylenevinylene) results in a drastic increase of permeability and diffusion coefficient of different diatomic and multi-atomic gases [132, 134, 135]. Vulcanizable rubbers were prepared using ROMP polymerization and copolymerization of chlorosilyl-substituted norbornenes [133, 144] and other cycloolefins [145] (see Figure 2.13-5).

Copolymerization of 1,5-cyclooctadiene with 10 mol% 5-(trichlorosilyl)norbornene in the presence of 15 mol% 1-vinylcyclohex-3-ene gave an oily product ($M_n \approx 1000$) that is an effective polymeric adhesion promoter for the coupling of rubber to siliceous fillers [144].

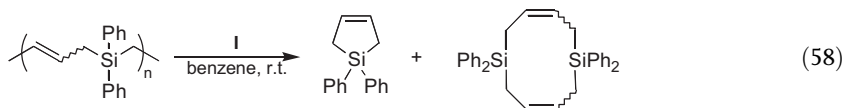
Polymerization of alkoxyisilylnorbornenes via ROMP in the presence of Re_2O_7/Al_2O_3 -, WCl_6 -, and $RuCl_3 \cdot 3H_2O$ -based systems has resulted in the formation of cross-linked insoluble polymers [51, 111]. Polynorbornenes containing carbazolypropyldimethylsilyl groups showed high thermal stability. A monomer containing two different polymerizable groups, 1-methyl-1-(norbornenyl)-1-silacyclobutane, was synthesized. Selective polymerization involving each type of reactive group, while keeping the other group intact, is possible for this monomer (Eq. (57)) [132, 138]. The remaining polymerizable functional group can be used for further polymer modification or for cross-linking.



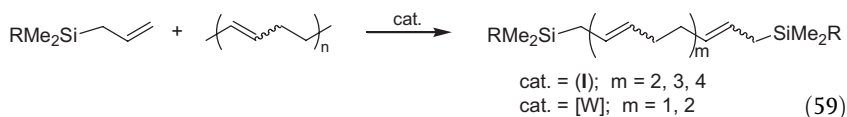
2.13.11

Degradation vs. Functionalization of Polymers

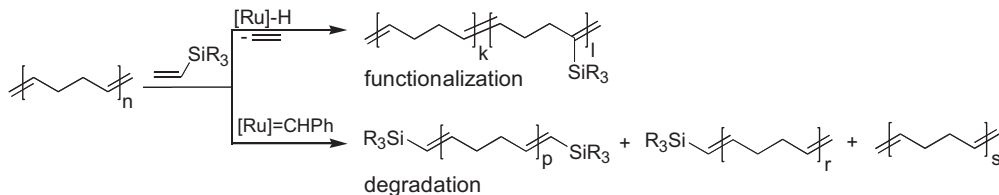
Polymers obtained via ROMP of silacyclopentene or ADMET of substituted diallylsilanes are readily degraded by dilution with toluene in the presence of **I** [69, 70]. This leads to the equilibrium mixture of silacyclopentane and cyclic dimers (Eq. (58)).



Synthesis of mass exact telechelic polybutadiene by the metathetic depolymerization of 1,4-polybutadiene via metathesis with monoallylsilanes in the presence of **I** and its tungsten analogue has been reported [139, 140].

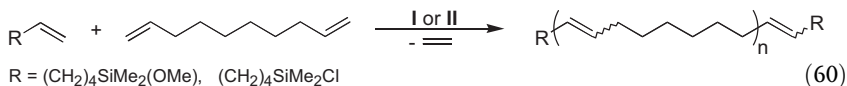


When polybutadiene ($M_w = 400,000$) underwent a treatment with vinyltriethoxysilane in the presence of Grubbs or Noels catalysts, a partial degradation was observed with the formation of silyl-terminated unsaturated oligomers ($M_w = 51,000$ and $113,000$, respectively [141]). However, if this procedure was performed at a higher temperature ($120\text{--}130\text{ }^\circ\text{C}$) in the presence of complexes containing or generating a Ru–H bond, exclusive functionalization of the =C–H bond of a polymer ($M_w \sim 500,000$) [142] was observed to proceed according to the silylative coupling reaction. A general illustration of the differences is given in Scheme 2.13-6.



Scheme 2.13-6. Functionalization vs. degradation of 1,4-polybutadiene.

Telechelic polyoctenamers were prepared via ADMET polymerization in the presence of 5-hexenylmethoxydimethylsilane or 5-hexenylchlorodimethylsilane as a chain limiter (Eq. (60)) [143].



The reaction is a convenient method for the synthesis of silyl group-terminated telechelic oligomers, which have several potential applications. Polycondensation of chlorodimethylsilane telechelomers with a hydroxy-terminated poly(dimethylsiloxane) macromonomer is just one example [143]. The introduction of reactive silyl groups into a polymer in terminal positions to get telechelic polymers has also been studied by Streck with WCl_6 based ill-defined catalysts [144, 145].

References

- For recent reviews see: (a) IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press: San Diego, **1997**; (b) *Alkene Metathesis in Organic Synthesis*, FÜRSTNER, A. Ed., Springer: Berlin, **1998**; (c) FÜRSTNER, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (d) BUCHMEISER, M. R. *Chem. Rev.* **2000**, *100*, 1565; (e) GRUBBS, R. H.; CHANG, S. *Tetrahedron* **1998**, *54*, 4413; (f) MARCINIEC, B.; PIETRASZUK, C. *Curr. Org. Chem.* **2003**, *7*, 691.
- COLVIN, E. W. *Silicon Reagents in Organic Synthesis*, Academic Press: London, **1988**.
- THOMAS, S. E. *Organic Synthesis. The Roles of Boron and Silicon*, Oxford Univ. Press: New York, **1991**.
- ZELDIN, M.; WYNNE, K. J.; ALLCOCK, H. R. *Inorganic and Organometallic Polymers: Macromolecules Containing Silicon, Phosphorus and other Inorganic Elements*, American Chemical Society: Washington, DC, **1988**.
- ZEIGLER, J. M.; FEARON, F. W. G. Eds. *Silicon-Based Polymer Science*, American Chemical Society: Washington, D.C. **1990**.
- BROOK, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*, Wiley and Sons: New York, **2000**.
- For recent reviews on the silylative coupling of olefins with vinylsilanes see: (a) MARCINIEC, B. In *Applied Homogeneous Catalysis with Organometallic Compounds*; CORNILS, B.; HERRMANN, W. A. Eds.; VCH: Weinheim, **2002**; Chapter 2.6. (b) REICHL, J. A.; BERRY, D. H. *Adv. Organomet. Chem.* **1998**, *43*, 203; (c) MARCINIEC, B. *Appl. Organomet. Chem.* **2000**, *14*, 527; (d) MARCINIEC, B. In *Ring Opening Metathesis Polymerisation and Related Chemistry*, KHOSRAVI, E.; SZYMAŃSKA-BUZAR, T. Eds.; Kluwer Acad. Publ.: Dordrecht, **2002**, p. 391 and (e) *ibid.* p. 331.
- KELLER, A.; MATUSIAK, R. *J. Mol. Catal. A: Chemical* **1996**, *104*, 213.
- SCHROCK, R. R.; DEPUÉ, R. T.; FELDMAN, J.; SHAVERIEN, C. J.; DEWAN, J. C.; LIU, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423.
- MARCINIEC, B.; GULIŃSKI, J. *J. Organomet. Chem.* **1984**, *266*, C19.
- MARCINIEC, B.; RZEJAK, L.; GULIŃSKI, J.; FOLTYNOWICZ, Z.; URBANIAK, W. *J. Mol. Catal.* **1988**, *46*, 329.
- MARCINIEC, B.; MACIEJEWSKI, H.; GULIŃSKI, J.; RZEJAK, L. *J. Organomet. Chem.* **1989**, *362*, 273.
- MARCINIEC, B.; PIETRASZUK, C. *J. Organomet. Chem.* **1991**, *412*, C1.
- SEKI, Y.; TAKESHITA, K.; KAWAMOTO, K. *J. Organomet. Chem.* **1989**, *369*, 117.
- MARCINIEC, B. In *Organosilicon and Bioorganosilicon Chemistry*, SAKURAI, H. Ed.; Ellis Horwood Ltd: New York, **1985**, p. 183.
- WAKATSUKI, Y.; YAMAZAKI, H.; NAKANO, M.; YAMAMOTO, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 703.
- MARCINIEC, B.; PIETRASZUK, C. *J. Chem. Soc., Chem. Commun.* **1995**, 2003.
- MARCINIEC, B.; PIETRASZUK, C. *Organometallics* **1997**, *16*, 4320.
- MARCINIEC, B.; WALCZUK-GUSCORA, E.; PIETRASZUK, C. *Catal. Lett.* **1998**, *55*, 125.
- MARCINIEC, B.; KOWNACKI, I.; CHADYNIK, D. *Inorg. Chem. Commun.* **1999**, *2*, 581.

- 21 MARCINIEC, B.; KUJAWA, M.; PIETRASZUK, C. *New J. Chem.* **2000**, 24, 671.
- 22 MARCINIEC, B.; KUJAWA, M.; PIETRASZUK, C. *Organometallics* **2000**, 19, 1677.
- 23 FEHER, F. J.; SOULIVONG, D.; EKLUND, A. G.; WYDHAM, K. D. *Chem. Commun.* **1997**, 1185.
- 24 PIETRASZUK, C.; MARCINIEC, B.; FISCHER, H. *Organometallics* **2000**, 19, 913.
- 25 PIETRASZUK, C.; FISCHER, H.; KUJAWA, M.; MARCINIEC, B. *Tetrahedron Lett.* **2001**, 42, 1175.
- 26 KUJAWA-WELTEN, M.; PIETRASZUK, C.; MARCINIEC, B. *Organometallics* **2002**, 21, 840.
- 27 KUJAWA-WELTEN, M.; MARCINIEC, B. *J. Mol. Catal. A: Chemical* **2002**, 190, 79.
- 28 CHATTERJEE, A. K.; MORGAN, J. P.; SCHOLL, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, 122, 3783.
- 29 PIETRASZUK, C.; MARCINIEC, B.; JANKOWSKA, M. *Adv. Synth. Catal.* **2002**, 344, 789.
- 30 PIETRASZUK, C.; FISCHER, H. *Chem. Commun.* **2000**, 2463.
- 31 MARCINIEC, B.; WALCZUK-GUŚCIORA, E.; PIETRASZUK, C. *Organometallics* **2001**, 20, 3423.
- 32 PIETRASZUK, C.; MARCINIEC, B.; JANKOWSKA, M. *Pol. Pat.* P-355875.
- 33 CHADYNIAR, D.; KROMPIEC, S.; PRUKAŁA, W.; MARCINIEC, B. (unpublished results).
- 34 MARCINIEC, B.; JANKOWSKA, M.; ZAJDLEWICZ, M.; CYTARSKA, J. (unpublished results).
- 35 ITAMI, Y.; MARCINIEC, B.; MAJCHRAZAK, M.; KUBICKI, M. *Organometallics* **2003**, 22, 1835.
- 36 ITAMI, Y.; MARCINIEC, B.; KUBICKI, M. (accepted for publication).
- 37 ITAMI, Y.; MARCINIEC, B.; KUBICKI, M. *Organometallics* (accepted for publication).
- 38 CROWE, W. E.; GOLDBERG, D. R.; ZHANG, Z. J. *Tetrahedron Lett.* **1996**, 37, 2117.
- 39 CROWE, W. E.; GOLDBERG, D. R. *J. Am. Chem. Soc.* **1995**, 117, 5162.
- 40 BLANCO, O. M.; CASTEDO, L. *Synlett* **1999**, 5, 557.
- 41 BOUZBOUZ, S.; DE LEMOS, E.; COSSY, J. *Adv. Synth. Catal.* **2002**, 344, 627.
- 42 BRÜMMER, O.; RÜCKERT, A.; BLECHERT, S. *Chem. Eur. J.* **1997**, 3, 441.
- 43 ROY, R.; DAS, S. K.; DOMINIQUE, R.; TRONO, M. C.; HERNANDEZ-MATEO, F.; SANTOYO-GONZALEZ, F. *Pure Appl. Chem.* **1999**, 71, 565.
- 44 ROY, R.; DOMINIQUE, R.; DAS, S. K. *J. Org. Chem.* **1999**, 64, 5408.
- 45 ENGELHARDT, F. C.; SCHMITT, M. J.; TAYLOR, R. E. *Org. Lett.* **2001**, 3, 2209.
- 46 TAYLOR, R. E.; ENGELHARDT, F. C.; SCHMITT, M. J.; YUAN, H. J. *Am. Chem. Soc.* **2001**, 123, 2964.
- 47 LANGER, P.; HOLTZ, E. *Synlett* **2002**, 110.
- 48 SESHADRI, H.; LOVELY, C. J. *Org. Lett.* **2000**, 2, 327.
- 49 SCHUSTER, M.; LUCAS, N.; BLECHERT, S. *Chem. Commun.* **1997**, 823.
- 50 FINKELSHTEIN, E. S.; USHAKOV, N. V.; PORTNYKH, E. B. *J. Mol. Catal.* **1992**, 76, 133.
- 51 FINKELSHTEIN, E. S.; MARCINIEC, B. In *Progress in Organosilicon Chemistry*; MARCINIEC, B.; CHOJNOWSKI, J. Eds.; Gordon and Breach: Amsterdam, **1995**, p. 445.
- 52 VDOVIN, V. M.; USHAKOV, N. V.; PORTNYKH, E. B.; FINKELSHTEIN, E. S.; ABASHKINA, N. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 33, 2121.
- 53 USHAKOV, N. V.; FINKELSHTEIN, E. S.; PORTNYKH, E. B.; VDOVIN, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 30, 2835.
- 54 BESPALOVA, N. B.; BOVINA, M. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 39, 172.
- 55 LEVEBvre, F.; LECONTE, M.; PAGANO, S.; MUTCH, A.; BASSET, J. M. *Polyhedron* **1995**, 14, 3209.
- 56 FINKELSHTEIN, E. S.; PORTNYKH, E. B.; USHAKOV, N. V.; VDOVIN, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 30, 641.
- 57 USHAKOV, N. V.; PORTNYKH, E. B.; PRITULA, N. A.; FINKELSHTEIN, E. Sh. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 38, 2797.
- 58 CHANG, S.; GRUBBS, R. H. *Tetrahedron Lett.* **1997**, 38, 4757.
- 59 MEYER, C.; COSSY, J. *Tetrahedron Lett.* **1997**, 38, 7861.

- 60 CASSIDY, J. H.; MARSDEN, S. P.; STEMPE, G. *Synlett* **1997**, 1411.
- 61 DENMARK, S. E.; YANG, S. M. *Org. Lett.* **2001**, 3, 1749.
- 62 LANDAIS, Y.; SURANGE, S. S. *Tetrahedron Lett.* **2001**, 42, 581.
- 63 FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, 114, 5426.
- 64 EVANS, P. A.; MURTHY, V. S. *J. Org. Chem.* **1998**, 63, 6768.
- 65 HOYE, T. R.; PROMO, M. A. *Tetrahedron Lett.* **1999**, 40, 1429.
- 66 BRIOT, A.; BUJARD, M.; GOUVERNEUR, V.; NOLAN, S. P.; MIOSKOWSKI, C. *Org. Lett.* **2000**, 2, 1517.
- 67 BOITEAU, J. G.; VAN DE WEGHE, P.; EUSTACHE, J. *Tetrahedron Lett.* **2001**, 42, 239.
- 68 HARRISON, B. A.; VERDINE, G. L. *Org. Lett.* **2001**, 3, 2157.
- 69 ANHAUS, J. T.; CLEGG, W.; COLLINGWOOD, S. P.; GIBSON, V. C. *J. Chem. Soc., Chem. Commun.* **1991**, 1720.
- 70 ANHAUS, J. T.; GIBSON, V. C.; CLEGG, W.; COLLINGWOOD, S. P. *Organometallics* **1993**, 12, 1780.
- 71 LECONTE, M.; PAGANO, S.; MUTCH, A.; LEFEBVRE, F.; BASSET, J. M. *Bull. Soc. Chim. France* **1995**, 132, 1069.
- 72 AHMAD, J.; FALCK-PEDERSEN, M. L.; UNDHEIM, K. J. *Organomet. Chem.* **2001**, 625, 160.
- 73 HOSHI, T.; YASUDA, H.; SANJI, T.; SAKURAI, H. *Bull. Chem. Soc. Jpn.* **1999**, 72, 821.
- 74 FORBES, M. D. E.; PATTON, J. T.; MYERS, T. L.; MAYNARD, H. D.; SMITH, JR. D. W.; SCHULZ, G. R.; WAGENER, K. B. *J. Am. Chem. Soc.* **1992**, 114, 10978.
- 75 MINGOTAUD, A. F.; HEROGUEZ, V.; SOUM, A. J. *Organomet. Chem.* **1998**, 560, 109.
- 76 MILLER, J. F.; TERMIN, A.; KOCH, K.; PISCOPIO, A. D. *J. Org. Chem.* **1998**, 63, 3158.
- 77 BURKE, S. D.; NG, R. A.; MORRISON, J. A.; ALBERTI, M. J. *J. Org. Chem.* **1998**, 63, 3160.
- 78 SCHUMAN, M.; GOUVERNEUR, V. *Tetrahedron Lett.* **2002**, 43, 3513.
- 79 WADA, K.; IZUHARA, D.; YAMADA, K.; SHIOTSUKI, M.; KONDO, T.; MITSUDO, T. *Chem. Commun.* **2001**, 1802.
- 80 HOVEYDA, A. H.; SCHROCK, R. R. *Chem. Eur. J.* **2001**, 7, 945.
- 81 ZHU, S. S.; CEFALO, D. R.; LA, D. S.; JAMIESON, J. Y.; DAVIES, W. M.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1999**, 121, 8251.
- 82 KIELY, A. F.; JERNELIUS, J. A.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2002**, 124, 2868.
- 83 WEATHERHEAD, G. S.; HORSER, J. H.; FORD, J. G.; JAMIESON, J. Y.; SCHROCK, R. R.; HOVEYDA, A. H. *Tetrahedron Lett.* **2000**, 41, 9553.
- 84 AEILTS, S. L.; CEFALO, D. R.; BONITATEBUS, JR. P. J.; HOUSER, J. H.; HOVEYDA, A. H.; SCHROCK, R. R. *Angew. Chem.* **2001**, 113, 1500; *Angew. Chem., Int. Ed.* **2001**, 40, 1452.
- 85 HULTZSCH, K. C.; BONITATEBUS, JR. P. J.; JERNELIUS, J.; SCHROCK, R. R.; HOVEYDA, A. H. *Organometallics* **2001**, 20, 4705.
- 86 TSANG, W. C. P.; SCHROCK, R. R.; HOVEYDA, A. H. *Organometallics* **2001**, 20, 5658.
- 87 HULTZSCH, K. C.; JERNELIUS, J. A.; HOVEYDA, A. H.; SCHROCK, R. R. *Angew. Chem.* **2002**, 114, 609; *Angew. Chem., Int. Ed.* **2002**, 41, 589.
- 88 BESPALOWA, N. B.; BOVINA, M. A.; SERGEEVA, M. B.; OPPENGEIM, V. D.; ZAIHIN, V. G. *J. Mol. Catal.* **1994**, 90, 21.
- 89 SCHNEIDER, M. F.; LUCAS, N.; VELDER, J.; BLECHERT, S. *Angew. Chem.* **1997**, 109, 257; *Angew. Chem., Int. Ed.* **1997**, 36, 257.
- 90 TALLARICO, J. A.; RANDALL, M. L.; SNAPPER, M. L. *Tetrahedron* **1997**, 53, 16511.
- 91 MICHAU, M.; PARRAIN, J. L.; SANTELLI, M. *Chem. Commun.* **1998**, 2567.
- 92 JUANG, A.; SCHERMAN, O. A.; GRUBBS, R. H.; LEWIS, N. S. *Langmuir* **2001**, 17, 1321.
- 93 KINGSBURY, J. S.; GARBER, S. B.; GIFTOS, J. M.; GRAY, B. L.; OKAMOTO, M. M.; FARRER, R. A.; FOURKAS, J. T.; HOVEYDA, A. H. *Angew. Chem.* **2001**, 113, 4381; *Angew. Chem., Int. Ed.* **2001**, 40, 4251.
- 94 LA, D. S.; SATTELY, E. S.; FORD, J. G.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2001**, 123, 7767.

- 95 LA, D. S.; FORD, J. G.; SATTELY, E. S.; BONITATEBUS, P. J.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603.
- 96 STRAGIES, R.; BLECHERT, S. *Synlett* **1998**, 169.
- 97 STRAGIES, R.; BLECHERT, S. *Tetrahedron* **1999**, *55*, 8179.
- 98 MARCINIEC, B.; LEWANDOWSKI, M. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 1443.
- 99 MARCINIEC, B.; LEWANDOWSKI, M. *J. Inorg. Organomet. Polym.* **1995**, *15*, 115.
- 100 MARCINIEC, B.; MAŁECKA, E. *Macromol. Rapid Commun.* **1999**, *20*, 475.
- 101 MAŁECKA, E.; MARCINIEC, B. (unpublished results).
- 102 MARCINIEC, B.; MAŁECKA, E.; ŚCIBIOREK, M. *Macromolecules* (accepted for publication).
- 103 MARCINIEC, B.; LEWANDOWSKI, M.; BIJPOST, E.; MAŁECKA, E.; KUBICKI, M.; WALCZUK-GUŚCIORA, E. *Organometallics* **1999**, *18*, 3968.
- 104 MARCINIEC, B.; LEWANDOWSKI, M. *Tetrahedron Lett.* **1997**, *38*, 3777.
- 105 MARCINIEC, B.; MAŁECKA, E.; MAJCHRZAK, M.; ITAMI, Y. *Macromol. Symp.* **2001**, *174*, 137.
- 106 MISE, T.; TAKAGUCHI, Y.; UMEMIYA, T.; SHIMIZU, S.; WAKATSUKI, Y. *Chem. Commun.* **1998**, 690.
- 107 SANDMAN, D. J. *Trends Polym. Sci.* **1994**, *2*, 44; *ibid.* **1997**, *5*, 71 and references therein.
- 108 MAJCHRZAK, M.; ITAMI, Y.; MARCINIEC, B.; PAWLUĆ, P. *Macromol. Rapid Commun.* **2001**, *22*, 202.
- 109 MAJCHRZAK, M.; MARCINIEC, B.; ITAMI, Y. (unpublished results).
- 110 MAJCHRZAK, M.; ITAMI, Y.; MARCINIEC, B.; PAWLUĆ, P. *Tetrahedron Lett.* **2000**, *41*, 10303.
- 111 FINKELSHTEIN, E. S. *Polymer Sci., Ser. B.* **1995**, *37*, 185.
- 112 SCHWENDEMAN, J. E.; CHURCH, A. C.; WAGENER, K. B. *Adv. Synth. Catal.* **2002**, *344*, 597.
- 113 WAGENER, K. B.; SMITH, JR. D. W. *Macromolecules* **1991**, *24*, 6073.
- 114 SMITH, JR. D. W.; WAGENER, K. B. *Macromolecules* **1993**, *26*, 1633.
- 115 SMITH, JR. D. W.; WAGENER, K. B. *Macromolecules* **1993**, *26*, 3533.
- 116 CUMMINGS, S. K.; SMITH, D. W.; WAGENER, K. B. *Macromol. Rapid Commun.* **1995**, *16*, 347.
- 117 CUMMINGS, S.; GINSBURG, E.; MILLER, R.; PORTMESS, J.; SMITH, JR. D. W.; WAGENER, K. In *Step Growth Polymers for High Performance Materials. New Synthetic Methods*; HEDRICK, J. L.; LABADIE, J. W. Eds.; Am. Chem. Soc. Symp. Series No. 624, American Chemical Society: Washington, DC, **1996**, Chapter 6.
- 118 ANDERSON, J. D.; CUMMINGS, S.; PORTMESS, J. D.; WAGENER, K. B. *Polymer Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1995**, *36*, 162.
- 119 CUMMINGS, S.; ANDERSON, J. D.; WAGENER, K. B. *Polymer Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1996**, *37*, 192.
- 120 CHURCH, A. C.; PAWLOW, J. H.; WAGENER, K. B. *Macromolecules* **2002**, *35*, 5746.
- 121 BRZEZIŃSKA, K. R.; SHITTER, R.; WAGENER, K. B. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 1544.
- 122 MAŁECKA, E.; MARCINIEC, B.; PIETRASZUK, C.; CHURCH, A. C.; WAGENER, K. B. *J. Mol. Catal. A: Chemical* **2002**, *190*, 27.
- 123 LAMMENS, H.; SARTORI, G.; SIFFERT, J.; SPRECHER, N. *Polymer Lett.* **1971**, *9*, 341.
- 124 STONICH, D. A.; WEBER, W. P. *Polymer Bull.* **1991**, *25*, 629.
- 125 ZHANG, X.; ZHOU, Q.; WEBER, W. P.; HORVATH, R. F.; CHAN, T. H.; MANUEL, G. *Macromolecules* **1988**, *21*, 1563.
- 126 SITA, L. R.; LYON, S. R. *J. Am. Chem. Soc.* **1993**, *115*, 10374.
- 127 ZHANG, L.; LEE, T. R. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1998**, *39*, 170.
- 128 KATZ, T. J.; LEE, S. J.; SHIPPEY, M. A. *J. Mol. Catal.* **1980**, *8*, 219.
- 129 GINSBURG, E. J.; GORMAN, C. B.; MARDER, S. R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 7621.
- 130 GORMAN, C. B.; GINSBURG, E. J.; MARDER, S. R.; GRUBBS, R. H. *Polym. Prepr. (Am. Chem. Soc. Div. Polym. Chem.)* **1990**, *31*, 386.

- 131 SAILOR, M. J.; GINSBURG, E. J.; GORMAN, C. B.; KUMAR, A.; GRUBBS, R. H.; LEWIS, N. S. *Science* **1990**, *249*, 1146.
- 132 MAKOVETSKY, K. L.; FINKELSHTEIN, E. S.; OSTROVSKAYA, I. Y.; PORTNYKH, E. B.; GORBACHEVA, L. I.; GOLBERG, A. I.; USHAKOV, N. Y.; YAMPOLSKY, YU. P. *J. Mol. Catal.* **1992**, *76*, 107.
- 133 ZIMMERMAN, M.; PAMPUS, G.; MAERTENS, D. *Ger. Offen.* **1976**, *2*, 460, 911; *Chem. Abstr.* **1976**, *85*, 95539.
- 134 FINKELSHTEIN, E. S.; MAKOVETSKY, K. L.; YAMPOLSKY, YU. P.; PORTNYKH, E. B.; OSTROVSKAYA, I. Ya.; KALIUZHNYI, N. E.; PRITULA, N. A.; GOLBERG, A. I.; YATSENKO, M. S.; PLATE, N. A. *Macromol. Chem.* **1991**, *192*, 1.
- 135 KAWAKAMI, Y.; TODA, H.; HIGASHINO, M.; YAMASHITA, Y. *Polymer J.* **1988**, *20*, 285.
- 136 FINKELSHTEIN, S. Sh.; PORTNYKH, E. B.; USHAKOV, N. V., MARCINIEC, B. In *Silicon-containing Polymers*, JONES. R. G. Ed.; Royal Soc. Chem. **1995**, 27.
- 137 STONICH, D. A.; WEBER, W. P. *Polymer Bull.* **1991**, *26*, 493.
- 138 FINKELSHTEIN, E. S.; USHAKOV, N. V.; PORTNYKH, E. B.; GREENGOLTS, M. L.; MAKOVETSKY, K. L.; BONDARENKO, G. N.; OSTROVSKAYA, I. Ya.; FILATOVA, M. P.; ANDREEV, E. A.; GOLBERG, A. I. *Polymer Sci.* **1993**, *35*, 291.
- 139 MARMO, J. C.; WAGENER, K. B. *Macromolecules* **1993**, *26*, 2137.
- 140 MARMO, J. C.; WAGENER, K. B. *Macromolecules* **1995**, *28*, 2602.
- 141 MARCINIEC, B.; LEWANDOWSKI, M.; GULIŃSKI, J.; NOELS, A. F.; DEMONCEAU, A.; MAŁECKA, E.; JAN, D. *Polymer* **2000**, *41*, 827.
- 142 MARCINIEC, B.; MAŁECKA, E.; GULIŃSKI, J.; GRUNDWALD-WYSPIAŃSKA, M.; LEWANDOWSKI, M. *Can. J. Chem.* **2002**, *79*, 775.
- 143 BRZEZIŃSKA, K. R.; WAGENER, K. B.; BURNS, G. T. *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 849.
- 144 STRECK, R. *J. Mol. Catal.* **1982**, *15*, 3.
- 145 STRECK, R.; WEBER, H. *Ger. Offen.* **1975**, *2*, 314, 543; *Chem. Abstr.* **1975**, *82*, 73848.

2.14

Commercial Applications of Ruthenium Metathesis Processes

Richard L. Pederson

2.14.1

Introduction

The use of olefin metathesis in the synthesis of biologically active compounds, fine chemicals, and polymer additives has grown rapidly in recent years. For example, many pharmaceutical companies have exploited metathesis reactions to produce novel platform structures [1]. Ring-closing metathesis reactions, and to a lesser extent, ring-opening metathesis reactions, have found increasing success as the key synthetic transformation in their synthetic routes [1, 2]. Recently the exploitation of olefin cross-metathesis has emerged as a valuable synthetic tool in commercial products [3]. Cross-metathesis methodologies have recently been shown to be highly effective in the synthesis of insect pheromones [4, 5], polymer additives [6], and fine chemicals, i.e., valuable synthetic intermediates such as novel α,β -unsaturated carbonyl systems [7, 8]. In this chapter, we will describe several cross-metathesis, ring-opening, and ring-closing metathesis reactions that have commercial potential as products for fine chemicals and pharmaceuticals.

2.14.2

Fine Chemicals

Patents and patent applications using olefin metathesis processes in fine chemical areas are much fewer in number compared with the patent literature for pharmaceutical applications. One reason for this is that the fine chemical opportunities to date have been small-niche applications, usually too small for larger corporations to develop. These products usually are not chemically unique, as in the pharmaceutical industry; therefore, they can be made by other competing technologies. Another possible reason is that the metathesis catalyst may be too expensive for many commodity-type applications. However, many of the barriers to commercialization will be eliminated as the metathesis catalysts are scaled up to multi-hundred kilogram quantities, which will allow for commercial opportunities in areas once thought of as uneconomical.

2.14.2.1

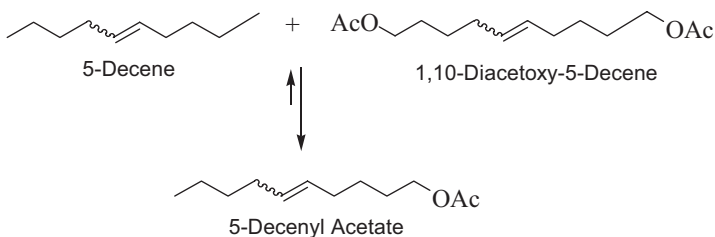
Agrochemicals: Insect Pheromones

Ruthenium metathesis methodology has been of particular success in the synthesis of insect pheromones [2f, 4, 5, 9, 10]. Insect pheromones are biologically active compounds used by the same species for communication. The use of the female's sex attractant to confuse the male and disrupt mating is an effective and environmentally friendly technique for controlling insect populations [11].

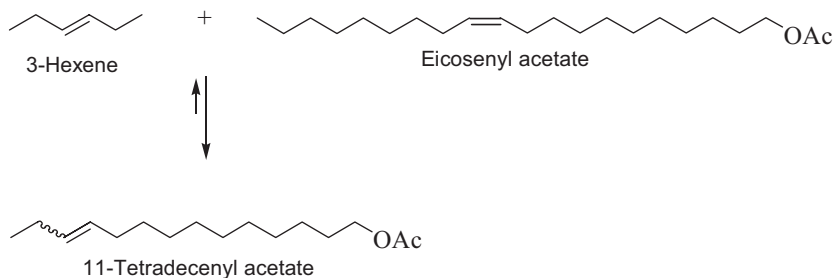
The advantages of using olefin metathesis to produce insect pheromones are as follows: most of the starting materials are commodity materials (e.g., seed oils, alpha olefins), the reactions can be run neat, the reactions can provide up to 50% reactor efficiencies, the unreacted starting materials are recycled, very little waste is produced, and the reactions are run under near-ambient temperatures [4]. These factors make insect pheromones attractive targets for commercialization.

Two attractive lepidopteran insect pheromone targets are those of the peach twig borer (*Anarsia lineatella*) and the omnivorous leafroller (*Platynota stultana*) [4, 5]. The peach twig borer is a pest of peaches, plums, nectarines, and almonds. The peach twig borer pheromone is an 83:17 ratio of E-5-decenyl acetate and E-5-decenol, although modest amounts of the Z-isomers have no effect on efficacy. Since metathesis reactions produce equilibrium mixtures, cross-metathesis of equal molar ratios of 5-decene with 1,10-diacetoxy-5-decene will produce a maximum yield of 50% of 5-decenyl acetate (Scheme 2.14-1). In these applications, the second-generation Grubbs' catalysts work particularly well [4]. Unreacted 5-decene with 1,10-diacetoxy-5-decene is readily recovered by vacuum distillation and recycled.

The omnivorous leafroller (OLR) is a pest of apples, grapes, pears, peaches, and nectarines. The OLR pheromone is an 82:18 ratio of E- to Z-11-tetradecenyl acetate. The synthesis of OLR pheromone is a particularly attractive target for metathesis because the metathesis reaction produces the pheromone with the desired (E to Z) isomeric ratio (Scheme 2.14-2). The two starting materials 3-hexene and 11-eicosenyl acetate were derived from commodity materials (3-hexene from 1-butene and 11-eicosenyl acetate from jojoba oil). Cross-metathesis of 4 equivalents of 3-hexene with 11-eicosenyl acetate produced an 84% conversion of 11-eicosenyl acetate to 11-tetradecenyl acetate. 11-Tetradecenyl acetate was isolated in 50% yields and >95% chemical purity, the major impurity being 9-octadecene [4].



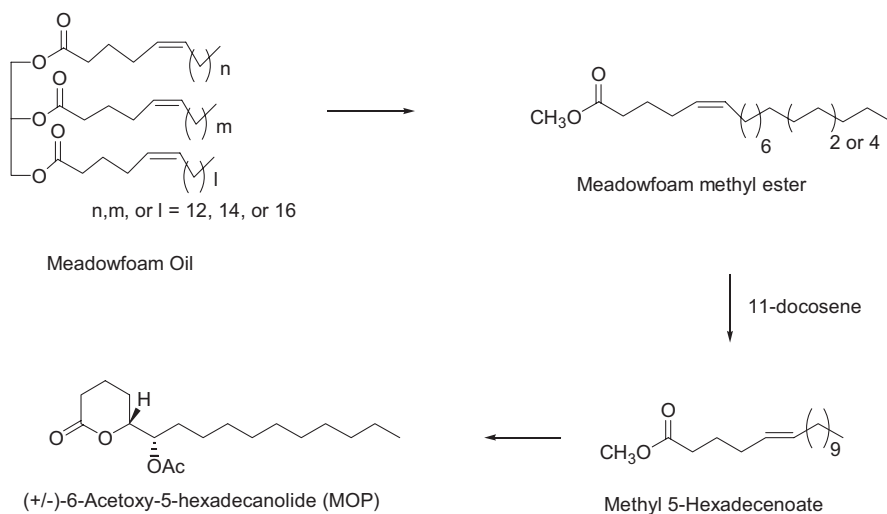
Scheme 2.14-1



Scheme 2.14-2

Synthesis of racemic (5R,6S)-6-acetoxy-5-hexadecanolide, the mosquito oviposition pheromone (MOP), is an attractive application and target for olefin metathesis [5b]. Pathogen-vectoring mosquitoes in the genus *Culex* secrete this natural substance when gravid female mosquitoes lay their eggs, thereby attracting other gravid females to that location. The use of synthetic MOP will enable mosquitoes carrying West Nile Virus and other dangerous causative agents to be controlled without the need of broadcast spraying of large urban areas with conventional pesticides. The use of nontoxic insect pheromones to disrupt normal mating patterns or as an attractant for capturing insects (e.g., in either mass-trapping or attract-and-kill techniques) in a localized area is well established.

The two key starting materials for MOP, 11-docosene and methyl 5-eicosenoate, were derived from 1-dodecene and meadowfoam oil, respectively [5b]. Meadowfoam oil is an attractive starting material because >95% of the fatty acid side chains contain unsaturation at carbon 5. Meadowfoam oil was esterified and subjected to cross-metathesis with 11-docosene to yield a 5:1 ratio of *E*:*Z* methyl 5-hexadecanoate (Scheme 2.14-3). Epoxidation, lactonization, and acetylation yields



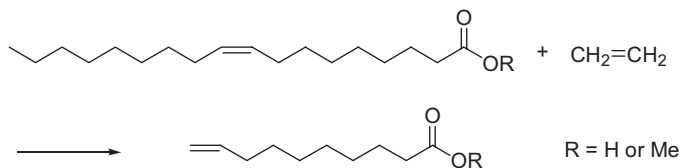
Scheme 2.14-3

MOP in 31% overall yield, >99% chemical purity, and >10:1 ratio of 5R:6S to 5S:6R diastereoselectivity [12]. MOP pheromone is being tested for efficacy in North America, South America, and Africa.

2.14.2.2

Polymer Additives

Dow has demonstrated an interest in using ruthenium olefin metathesis to create value added products from commodity starting materials. Dow's patent application [6] describes the ethenolysis of methyl oleate and oleic acid, with ruthenium catalysts containing a chelating ligand, to yield 1-decene and methyl 9-decenoate or 9-decenoic acid (Scheme 2.14-4). α -Olefins find utility in the manufacturing of poly(olefin) polymers, i.e., 1-decene is the major component of synthetic motor oils and lubricants [13]. Ester-functionalized α -olefins can be hydrolyzed to the acid-functionalized α -olefins, which find utility in thermoset polymer applications such as in urethanes and epoxy resins.



Scheme 2.14-4

2.14.2.3

Fuel Additives

Sasol has reported the conversion of C₄–C₁₀ alkene streams into C₆–C₁₈ alkenes [14] from a Fischer-Tropsch light oils process (Scheme 2.14-5). These new C₆–C₁₈ alkenes are useful in preparing distillate fuel compositions. These products are also isomerized to increase the octane value and lower the pour, cloud, and smoke points.

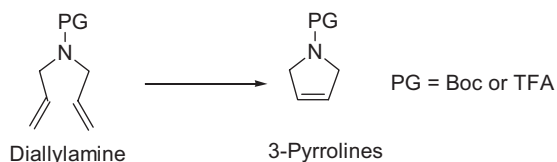


Scheme 2.14-5

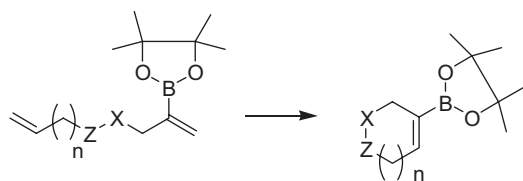
2.14.2.4

Drug Discovery

A particularly successful application of olefin metathesis was ring-closing metathesis (RCM) of *N*-Boc or *N*-TFA diallylamine to yield *N*-protected 3-pyrrolines



Scheme 2.14-6

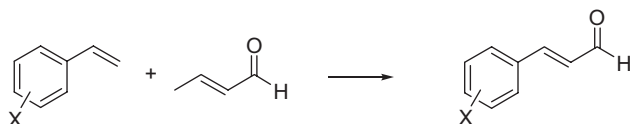


$n = 0, 1, 2$

$X = \text{CH}_2, \text{O}, \text{N-Boc}$

$Z = \text{CH}_2, \text{CH-Ph}, \text{C}(\text{CH}_3)_2$

Scheme 2.14-7



$X = \text{F}, \text{Cl}, \text{AcO}, \text{Me}, \text{NO}_2, \text{etc....}$

Scheme 2.14-8

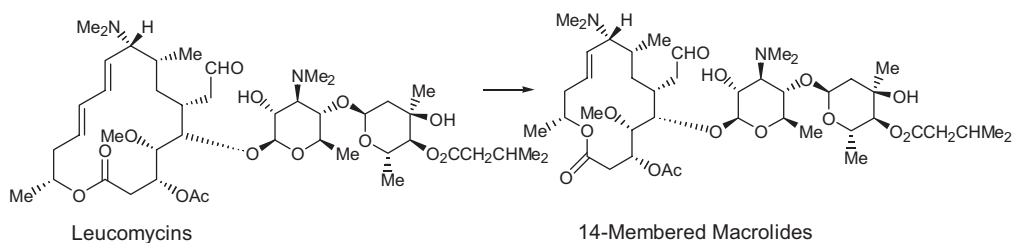
(Scheme 2.14-6), which are useful intermediates for drug discovery. Literature conditions describe RCM of 10-mM concentrations of protected diallylamine [15]. However, in the synthesis of several kilograms of products, these metathesis reactions were run neat to produce high isolated yields (>90%) and high chemical purity (>98%) of the desired *N*-protected 3-pyrrolines [16].

Examples of structural motifs that are easily synthesized with metathesis but are difficult to synthesize by traditional methods include Renaud's [17] synthesis of vinyl borate esters (Scheme 2.14-7) and Chatterjee's [18a,b] efficient synthesis of novel substituted cinnamaldehydes (Scheme 2.14-8). Vinyl borates are useful in Suzuki coupling reactions, and novel substituted cinnamaldehydes are useful in OrganoCatalyst™ reactions [18c,d].

2.14.3

Pharmaceutical Applications

The recent patent literature has seen an explosion of patents and patent applications using olefin metathesis processes in the pharmaceutical and drug-discovery



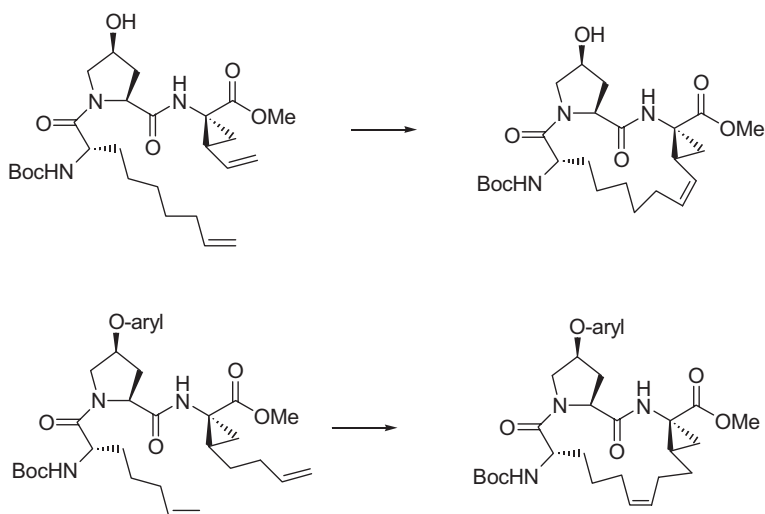
Scheme 2.14-9

areas. Below is a summary of the processes that have the potential to become commercial in the next 3–5 years.

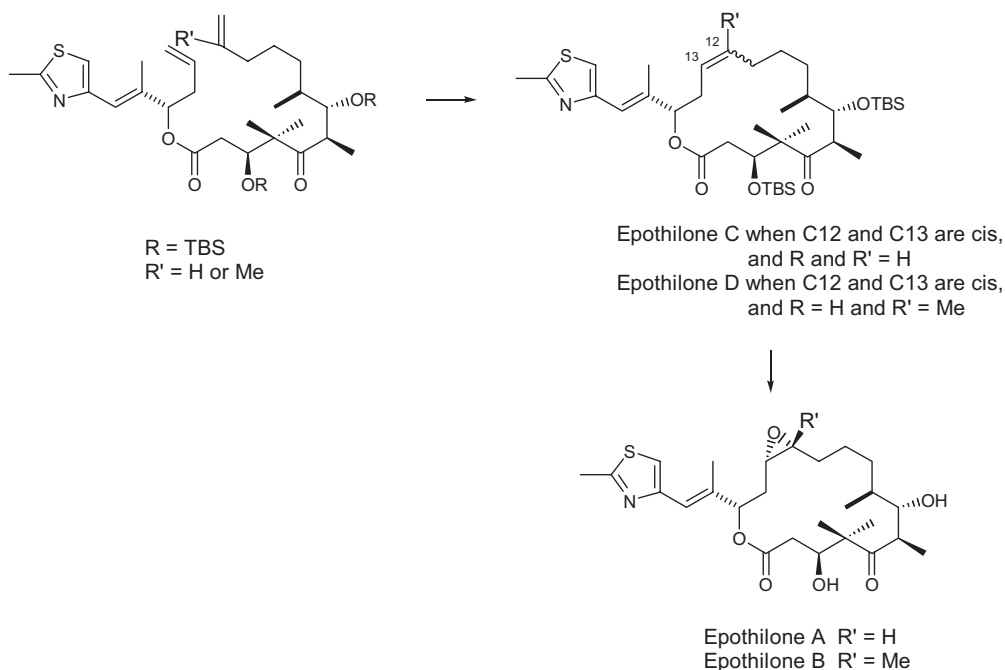
Enanta Pharmaceuticals has reported an ingenious use of olefin metathesis to produce a novel class of 14-membered macrolides [19], which are used in treating bacterial infections (Scheme 2.14-9). In Enanta's processes, 16-membered leucomycin derivatives are subjected to ROM-CM-RCM with short-chained α -olefins (i.e., 1-hexene, ethylene, isobutylene) to yield the novel 14-membered macrolides. One specific example is shown in Scheme 2.14-9; 17 metathesis reaction examples were reported.

Boehringer Ingelheim reported RCM applications to produce macrocyclic peptides that are active against the NS3 protease of the hepatitis C virus [1c]. Their processes include seven examples of RCM to yield the novel 15-membered macrolides; two of the seven examples are shown in Scheme 2.14-10. It is reported that the macrocycles are formed with high *cis* selectivity.

The syntheses of epothilones have generated a great deal of interest in both their use as microtubule-stabilizing cytotoxic anticancer agents and their syn-



Scheme 2.14-10



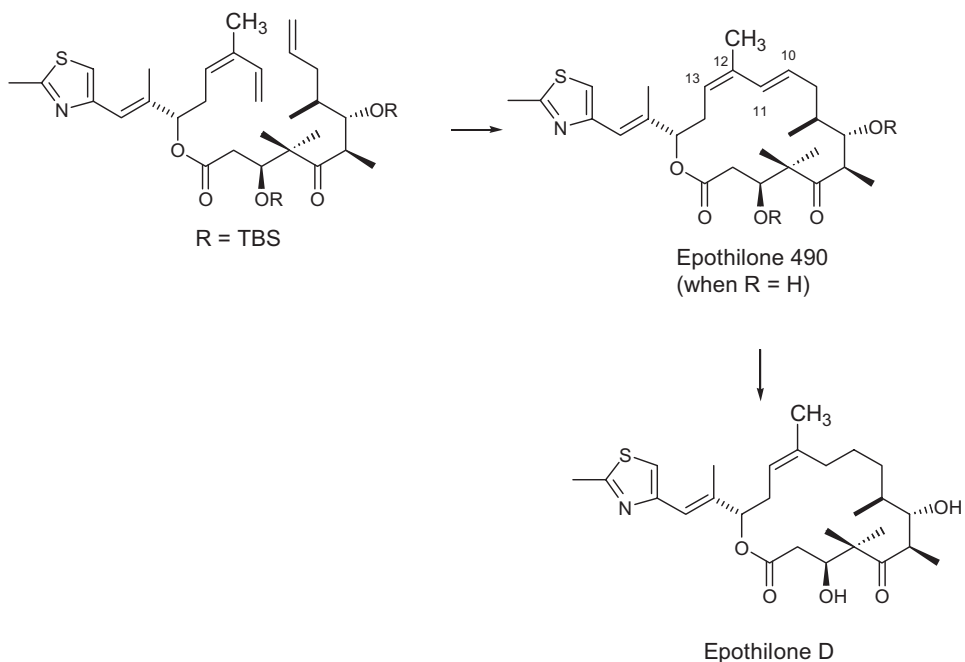
Scheme 2.14-11

theses. Recent SciFinder Scholar searches on epothilones A and B yielded 218 hits each, while epothilone C yielded 85 hits and epothilone D yielded 105 hits. Many of the hits related to synthesis of epothilone and its derivatives. The groups of Schinzer [20], Danishefsky [21], and Nicolaou [22] will be focused on for their syntheses of epothilones using RCM methodologies (see Appendino [23] for an earlier review of the synthetic routes, including RCM strategies). A key macrocyclization step in each of these group's synthetic routes included RCM to form the *cis* C12–C13 double bond (Scheme 2.14-11). A limitation of the RCM methodology was the preferentially *trans* geometry of the newly formed C12–C13 double bond.

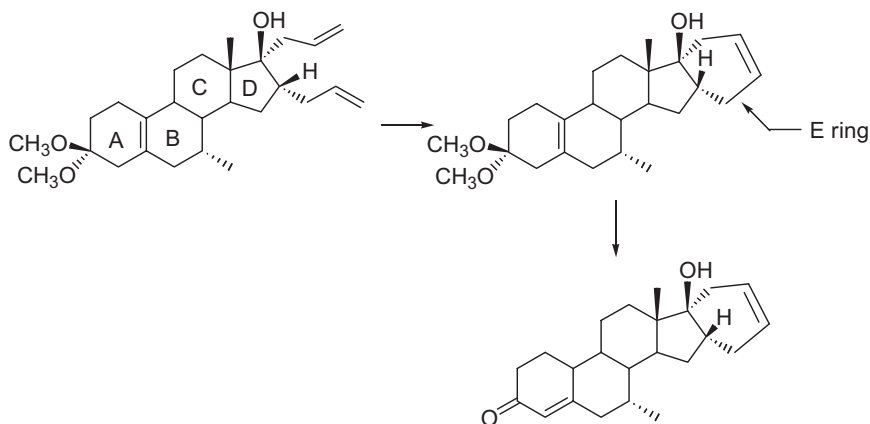
Danishefsky's group has overcome this limitation by setting the C12–C13 *cis*-double bond geometry then RCM at C10–C11, followed by selective reduction of epothilone 490 with diimide to yield epothilone D in 86% yields [24] (Scheme 2.14-12). Kosan Biosciences Inc. is exploring the commercialization of epothilone D, which inhibits cancer cells by the same mechanism as paclitaxel and is effective against paclitaxel-resistant tumors in *in vitro* and *in vivo* animal models [25].

Akzo Nobel reported the selective estrogen activities and synthesis of steroid-type compounds having contraceptive and anti-osteoporosis activity [26]. Their invention comprises the synthesis of an E-ring by RCM, sharing atoms at C16 and C17 of a steroid D-ring (Scheme 2.14-13). Three RCM reactions were reported.

DuPont [27] and Bristol-Myers Squibb [28] have reported the syntheses of novel lactam compounds that inhibit the production of A β -peptide, an amyloid precursor



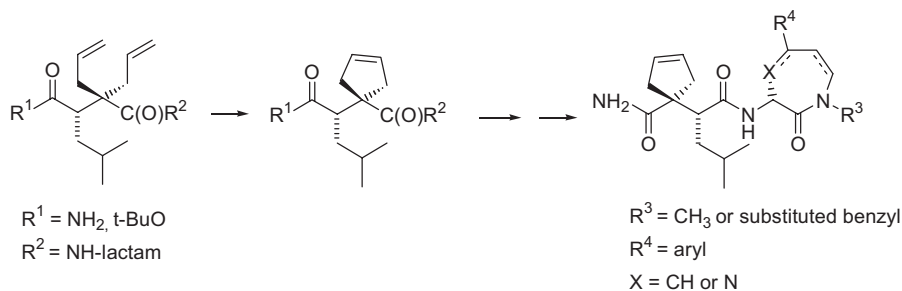
Scheme 2.14-12



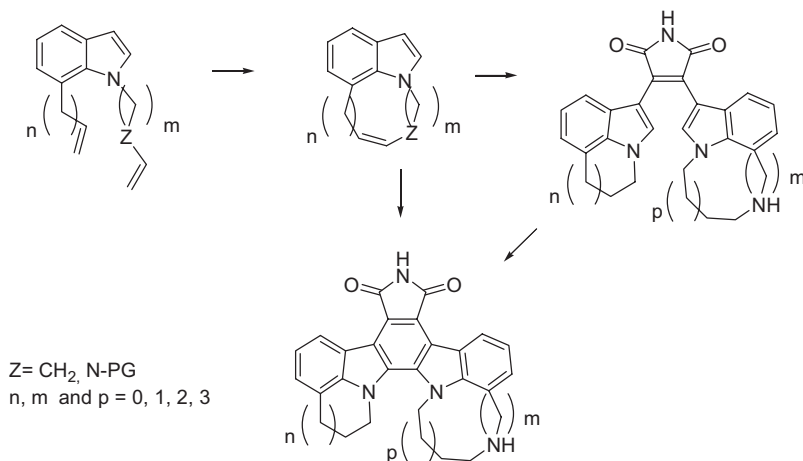
Scheme 2.14-13

protein, thereby acting to prevent the formation of neurological deposits of amyloid protein. These novel lactam compounds can be used in the treatment of neurological disorders related to β -amyloid production, such as Alzheimer's disease and Down's syndrome.

The RCM of the diallyl intermediates yields the cyclopentene intermediates, which were incorporated into lactam-peptide compounds. DuPont's application



Scheme 2.14-14



Scheme 2.14-15

reports six RCM reactions, and Bristol-Myers Squibb's application reports seven RCM reactions (Scheme 2.14-14).

Eli Lilly's metathesis program is involved in the synthesis of compounds for the treatment of proliferative diseases [29]. Cancer has been recognized as a disease of uncontrolled cell proliferation. Novel therapeutics, developed by RCM technology, are useful in the treatment of cell proliferation by selectively inhibiting specific stages of cell replication. Cell replication is controlled by specific cyclin-dependent kinases (CDK). A class of indole-type compounds has been found to be active against CDK (Scheme 2.14-15). Several examples of RCM reactions have been reported.

GSK has reported the synthesis of a novel class of 4-amino-azepen-3-one protease inhibitors of cathepsin K [30]. These compounds are useful in the treatment of diseases of excesses bone, cartilage, or matrix degeneration, including osteoporosis, gingivitis, periodontitis, arthritis, osteoarthritis and rheumatoid arthritis, Paget's disease, and metabolic bone disease. The synthesis of the key 4-amino-azepen-3-one intermediate was accomplished by RCM from *t*-butyl or



R_2 = amino acid side chain

R^3 = amide, peptide, protecting group

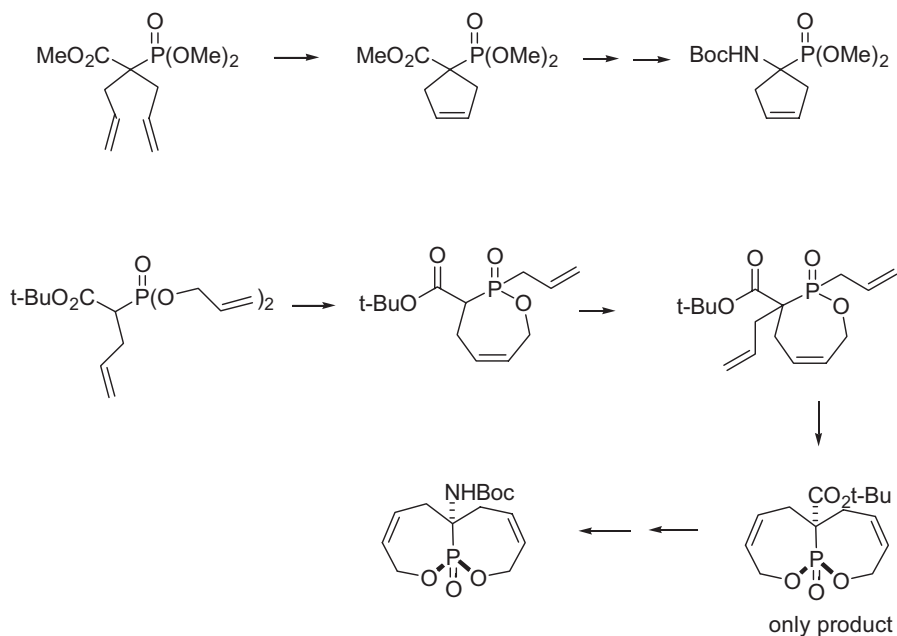
Scheme 2.14-16



Scheme 2.14-17

benzyl *N*-allylcarbamates. Epoxidation, epoxide ring opening with azide, reduction, and oxidation yields 4-amino-azepen-3-one. These intermediates were converted to 279 novel peptide compounds (Scheme 2.14-16).

Amgen has reported the synthesis of novel carboxylic acid substituted 7- and 8-membered heterocycles in several patents and patent applications [31] (Scheme 2.14-17). These compounds are effective for prophylaxis and treatment of inflammation, tissue degradation, cancer, fibrosis, and related diseases. These compounds inhibit metalloproteinase enzymes (e.g., collagenases, stromelysin, gelatinases, and TNF convertases) that may contribute to the onset of or exacerbate connective tissue degradation disease states. Over 400 examples of 7-membered and 8-membered heterocycles, derived from RCM products, have been reported.



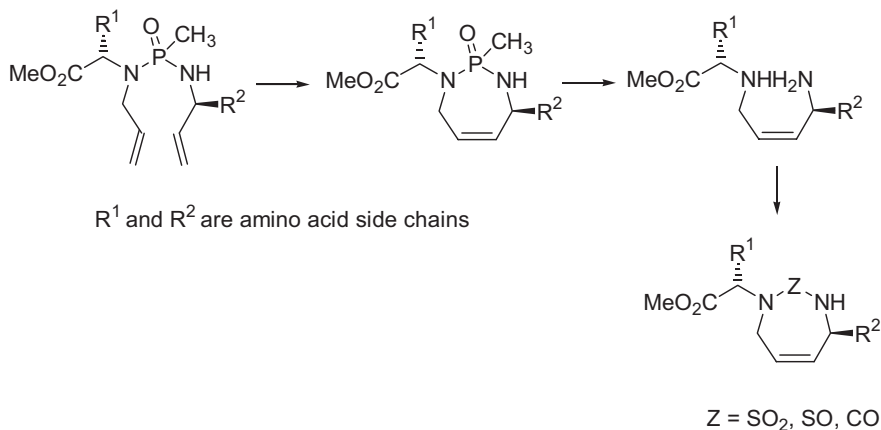
Scheme 2.14-18

Professor Paul Hanson, University of Kansas, has developed novel RCM technologies of phosphorus- [32] and sulfur-containing [33] heterocycles. These compounds may find uses in treating HIV or as thrombin inhibitors, fibrinogen receptor antagonists, endothelin-A receptor inhibitors, glycoprotein IIB/IIIA inhibitors, antibiotics, antitumor agents, matrix metalloproteinase inhibitors, or herbicides in agrochemical applications. Dr. Hanson's technology includes novel cyclopentenyl phosphonates and α -aminophosphonates [34] (Scheme 2.14-18); unsymmetrical phosphonamides [32a, 35]; 1,2,7-thiadiazepane-1-oxides, phosphonamides, and ureas [32b] (Scheme 2.14-19); symmetrical sulfamindes [33a, 36]; 1,2,7-thiadiazepane-1-oxides, phosphonamides, and ureas [32b] (Scheme 2.14-20); and allyl sulfonamides and vinyl sulfonamides [33b] (Scheme 2.14-21).

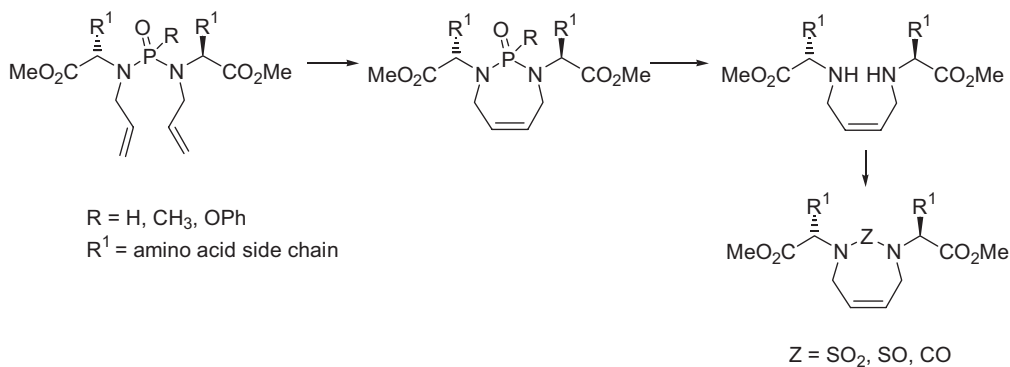
Sepracor has developed novel solid-supported synthesis of cyclic libraries of antibacterial agents using metathesis [37]. Eight ring-opening metathesis reactions are reported; two examples are shown in Scheme 2.14-22.

Another example of biologically active structural motifs that are easily made with metathesis but are difficult to synthesize by traditional methods includes Barrett et al.'s publication [38] of the synthesis of potentially bioactive β -lactams by RCM. Dienes suitable for RCM were prepared via Ireland-Claisen rearrangement and subjected to RCM to yield [5.2.0] and [6.2.0] bicycles (Scheme 2.14-23). Further elaborations yielded the potentially bioactive β -lactam-containing systems.

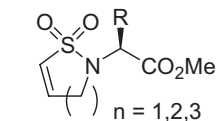
Merck chemists have reported the synthesis of an NK-1 receptor antagonist, in seven steps, from phenylalanine methyl ester [39]. NK-1 receptor antagonists are



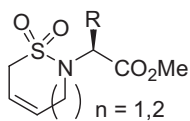
Scheme 2.14-19



Scheme 2.14-20



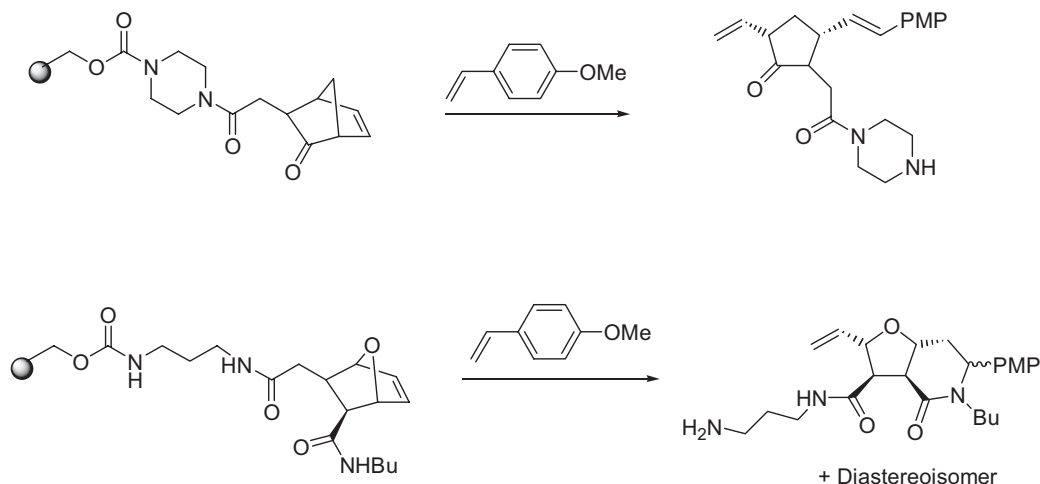
Vinyl Sulfonamides



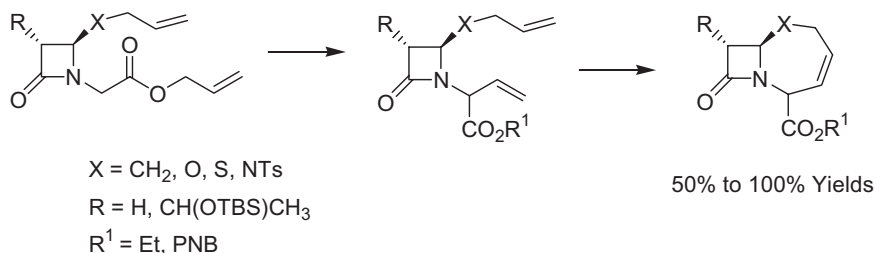
Allyl Sulfonamides

$R = \text{amino acid side chains}$

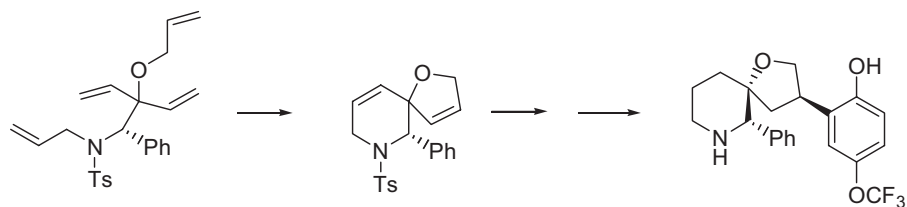
Scheme 2.14-21



Scheme 2.14-22



Scheme 2.14-23

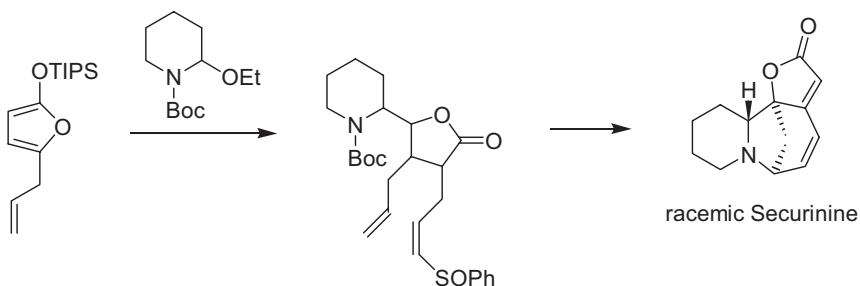


Scheme 2.14-24

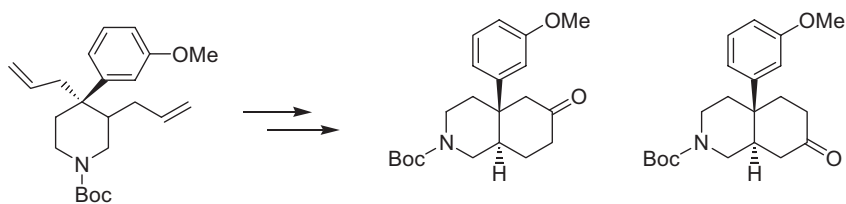
useful in the treatment of migraine headaches. The key step was the double RCM reaction to yield the spiro-diene in 86% yield and 70% ds (Scheme 2.14-24).

Pfizer chemists have reported the synthesis of securinine, an alkaloid that possesses CNS biological activity as a GABA receptor antagonist (Scheme 2.14-25). Securinine is a member of the Securinega family of alkaloids with interesting structural features of an indolizidine skeleton, a butenolide moiety, and an azabicyclo [3.2.1] system [40].

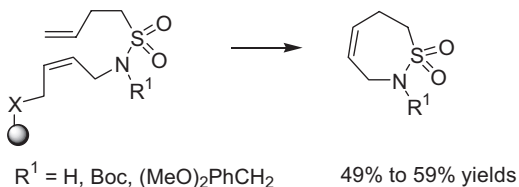
Pfizer chemists have also reported the synthesis 4a-aryloxydecahydroisoquinolines via RCM [41] (Scheme 2.14-26). These compounds represent structural frag-



Scheme 2.14-25



Scheme 2.14-26

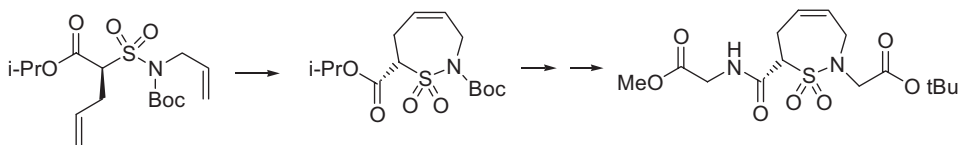


Scheme 2.14-27

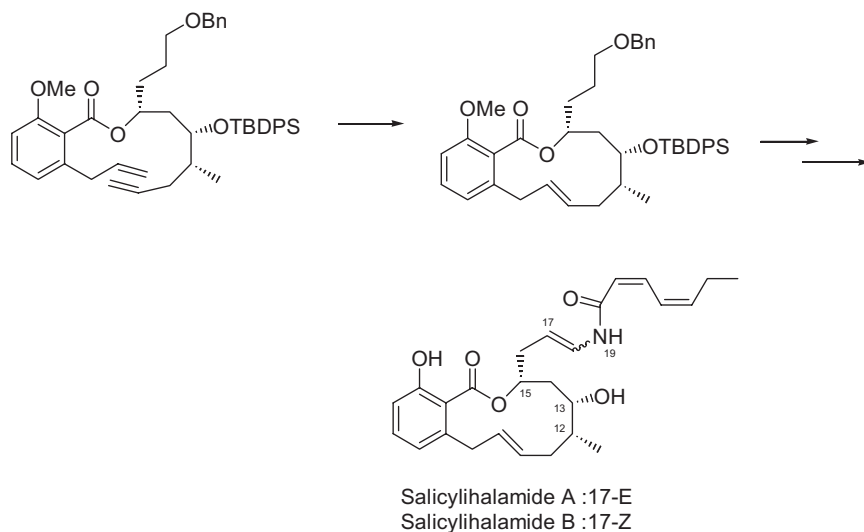
ments of morphine with significant pharmacological activity, exhibit potent affinity for the μ opiate receptor, and possess antinociceptive properties.

Merck Sharp & Dohme chemists have reported the RCM cyclizative release of resin-bound sulfonamides [42] (Scheme 2.14-27). Seven-membered cyclic sulfonamides have attracted considerable interest as analogues of known biologically active nitrogen-containing heterocycles with HIV protease inhibition [43], bile acid uptake inhibition [44], and herbicide activity [45]. Three RCM products have been synthesized, and optimization of RCM reactions was described.

DuPont chemists have also used RCM to synthesize 7-membered sulfonamide analogues [46] (Scheme 2.14-28). The sulfonamide moiety is a common feature of



Scheme 2.14-28



Scheme 2.14-29

combinatorial libraries. The tetrahedral sulfonamide provides an enzyme hydrolytically stable transition-state amide bond analogue, thus explaining its ubiquitous biological activity.

Several groups have published the total synthesis of salicylihalamides A and B [47], and Biochem Pharma Inc. chemists recently reported the enantioselective total synthesis of salicylihalamides A [47b,c] and B via RCM [47a] (Scheme 2.14-29). Salicylihalamides A and B are novel cytotoxic macrolides that may possess a novel mechanism of action against NCI 60 cell line human tumor assay.

2.14.4

Future Directions for Metathesis

One of the more exciting new directions involving ruthenium metathesis is tandem catalytic reactions. Tandem reactions allow for rapid generation of target compounds efficiently without the need to purify at each step. The Wagener, Snapper, and Grubbs groups have recently demonstrated this concept.

Wagener's group [48] initially demonstrated the tandem reaction with homogeneous cross-metathesis reaction followed by the addition of silica gel to yield a heterogeneous hydrogenation catalyst. This process was used to prepare commercially relevant polyethylene-based materials, e.g., sequence-ordered ethylene/CO₂ and ethylene/CO copolymers and telechelic polyethylene.

Snapper's group [49] has reported RCM olefin-isomerization reactions to yield cyclic enol ethers. Cyclic enol ethers are important in the synthesis of bioactive compounds including glycals [50], polyether antibiotics [51], natural products [51], and nucleoside antibiotics [52]. Following RCM, forming gas was introduced that

generated the isomerization-active species. The isomerization of the corresponding allyl ethers to enol ethers proceeded smoothly and in good yields.

Grubbs' group has demonstrated two tandem reaction sequences. The first was an elegant tandem catalysis sequence used in the total synthesis of (R)-(-)-muscone [53]. This reaction sequence includes RCM, oxidation of a secondary alcohol to a ketone with transfer dehydrogenation, and hydrogenation of the newly formed olefin. All three reactions used the same ruthenium metal originally used in the RCM reaction. The second tandem reaction demonstrated ROMP, atom-transfer radical polymerization, and hydrogenation to form novel polymers efficiently [54].

Another exciting direction is enantioselective ruthenium metathesis reactions with chiral metathesis catalysts. The idea of using chiral ruthenium metathesis catalysts has been demonstrated by the Hoveyda [55] and Grubbs [56] groups. Hoveyda's chiral catalyst was reported to produce >98% *ee* on AROM/CM of tricyclic norbornenes. Grubbs' chiral catalyst was reported to yield 90% *ee* on desymmetrization of triene systems. Both chiral catalysts are highly specific for certain structural motifs in order to obtain high enantioselectivity. As the mechanism becomes better understood, more efficient chiral ligands can be synthesized and more efficient chiral metathesis catalysts will be developed.

As demonstrated by the tandem examples, with the judicious choice of desired reaction steps, two to three reaction processes can be accomplished with the same catalyst to efficiently yield the target compound. Chiral ruthenium metathesis catalysts are still in their infancy, and it will be interesting to see them grow and mature as useful enantioselective catalysts. These are a few of the many expected examples that should appear in the literature within the next 5 years.

2.14.5

Summary

This chapter describes the efficient syntheses of several pharmaceutical, fine chemical, and agrochemical compounds, produced via olefin metathesis methodologies. Examples include the synthesis of biologically active epothilones, macrocyclic peptides, cyclic sulfonamides, novel macrolides, insect pheromones, and polymer additives. These examples demonstrate that olefin metathesis is and will continue to be a powerful synthetic tool to produce carbon-carbon double bonds.

In the past decade, olefin metathesis has had a huge influence on the field of organic chemistry. Rarely has a new catalyst technology been so eagerly accepted and incorporated into reaction schemes. Ruthenium metathesis has seen a remarkable progression, starting from the early dichloro(3,3-diphenyl-2-propenylidene) bis(triphenylphosphine) ruthenium catalysts that catalyzed only ROMP of highly strained olefins, to the very active [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro (phenylmethylene) (tricyclohexylphosphine) ruthenium and [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro (o-isopropoxyphenylmethylene) ruthenium catalysts that catalyzed the cross-metathesis

of unstrained, electron-deficient α -olefins. It will be exciting to see what the next decade of olefin metathesis reactions will yield and what new tandem reaction sequences and chiral metathesis catalysts will be reported.

References

- 1 a) M. D. CUMMINGS, R. W. MARQUIS JR., Y. RU, S. K. THOMPSON, D. F. VEBER, D. S. YAMASHITA (Smithkline Beecham Corp.) WO 01/70232 A1, **2001**; b) R. W. MARQUIS JR., Y. RU, D. F. VEBER, M. D. CUMMINGS, D. S. YAMASHITA (Smithkline Beecham Corp.) WO 00/38687, **2000**; c) Y. S. TSANTRIZOS, D. R. CAMERON, A.-M. FAUCHER, E. GHIRO, N. GOUDREAU, M. LLINAS-BRUNET (Boehringer Ingelheim Ltd.) WO 00/59929, **2000**; d) D. A. HEERDING (Smithkline Beecham Corp.) WO 00/12515, **2000**; e) D. C. HARROWVEN, M. C. LUCAS, P. D. HOWES, *Tetrahedron Lett.* **2000**, 41, 8958–8987; f) S. LIRAS, M. P. ALLEN, J. F. BLAKE, *Org. Lett.* **2001**, 3, 3483–3486; g) C. J. CREIGHTON, A. B. REITZ, *Org. Lett.* **2001**, 3, 893–895; h) D. J. WALLACE, J. M. GOODMAN, D. J. KENNEDY, A. J. DAVIES, C. J. COWDEN, M. S. ASHWOOD, I. F. COTTRELL, U.-H. DOLLING, P. J. REIDER, *Org. Lett.* **2001**, 3, 671–674.
- 2 a) R. H. GRUBBS, S. J. MILLER, G. C. FU, *Acc. Chem. Res.* **1995**, 28, 446; b) M. SCHUSTER, S. BLECHERT, *Angew. Chem.* **1997**, 109, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2067; c) S. K. ARMSTRONG, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371; d) S. BLECHERT, *Pure Appl. Chem.* **1999**, 71, 1393; e) S. KUROSAWA, M. BANDO, K. MORI, *Eur. J. Org. Chem.* **2001**, 23, 4395–4399; f) M. SCHOLL, R. H. GRUBBS, *Tetrahedron Lett.* **1999**, 40, 1425–1428.
- 3 H. E. BLACKWELL; D. J. O'LEARY; A. K. CHATTERJEE, R. A. WASHERFELDER; D. A. BUSSMANN; R. H. GRUBBS, *J. Am. Chem. Soc.* **2000**, 122, 58–71.
- 4 R. L. PEDERSON; I. M. FELLOWS; T. A. UNG, H. ISHIHARA, AND S. P. HAJELA, *Advanced Synthesis & Catalysis* **2002**, 344, 728–735.
- 5 a) R. L. PEDERSON, R. H. GRUBBS, (TillieChem, Inc.) U.S. Patent 6,219,019, **2001**; b) R. L. PEDERSON, R. H. GRUBBS (TillieChem, Inc.) WO 01/36368 A2, **2001**.
- 6 T. H. NEWMAN; C. L. RAND; K. A. BURDETT; R. R. MAUGHON; D. L. MORRISON; E. P. WASSERMAN (DOW Global Tech. Inc.) WO 02/76920, **2002**.
- 7 T. L. CHIO, C. H. LEE, A. K. CHATTERJEE, R. H. GRUBBS, *J. Am. Chem. Soc.* **2001**, 123, 10417–10418; A. K. CHATTERJEE, J. P. MORGAN, M. SCHOLL, R. H. GRUBBS, *J. Am. Chem. Soc.* **2000**, 122, 3783–3784.
- 8 A. FÜRSTNER, K. LANGEMANN, N. KINDLER (Studiengesellschaft Kohle MBH) U.S. Patent 5,936,100, **1999**.
- 9 A. FÜRSTNER, *Angew. Chem.* **2000**, 112, 3140–3172; *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 3012–3043.
- 10 a) S. D. BURKE, N. MÜLLER, C. M. BEAUDRY, *Org. Lett.* **1999**, 1, 1827–1829; b) S. D. BURKE, E. A. VOIGHT, *Org. Lett.* **2001**, 3, 237–240; c) M. L. RANDALL, J. A. TALLARICO, M. L. SNAPPER, *J. Am. Chem. Soc.* **1995**, 117, 9610–9611.
- 11 P. E. HOWSE, I. D. R. STEVENS, O. T. JONES, *Insect Pheromones and their Use in Pest Management*, Chapman & Hall, New York, **1998**, 314–338.
- 12 R. L. PEDERSON; C. W. LEE; T. A. UNG; H. ISHIHARA, Book of Abstracts, 224th ACS National Meeting, Boston, MA, August 18–22, **2002**, ORGN-237.
- 13 Examples are J. A. BRENNAN (Mobil Oil Corp.) US 3997621, **1976**; W. E. GARWOOD; Q. N. LE; J. SHIM; S. S. WONG (Mobil Oil Corp.) US 5008460, **1991**; L. R. RUDNICK (Mobil Oil Corp.) US 5171908, **1992**.
- 14 J. M. BOTHA; J. P. K. REYNHARADT; C. VAN SCHALKWYK; H. C. VOSLOO (Sasol Tech. (Pty) Ltd., S. Afr.) WO 01/46096, **2001**.
- 15 G. C. FU; R. H. GRUBBS, *J. Am. Chem. Soc.* **1993**, 115, 9856; G. C. FU; R. H. GRUBBS, *J. Am. Chem. Soc.* **1993**, 115,

- 3800; G. C. FU; R. H. GRUBBS, *J. Am. Chem. Soc.* **1992**, 114, 7324; G. C. FU; R. H. GRUBBS, *J. Am. Chem. Soc.* **1992**, 114, 5426.
- 16 R. L. PEDERSON unpublished results, 2002.
- 17 J. RENAUD; S. G. OUELLET, *J. Am. Chem. Soc.* **1998**, 120, 7995.
- 18 a) A. K. CHATTERJEE; D. P. SANDERS; R. H. GRUBBS, *Org. Lett.* **2002**, 4, 1939; b) A. K. CHATTERJEE; F. D. TOSTE; T.-L. CHOI; R. H. GRUBBS, *Advanced Synthesis & Catalysis* **2002**, 344, 634; c) J. F. AUSTIN; D. W. C. MACMILLAN, *J. Am. Chem. Soc.* **2002**, 124, 1172; d) N. A. PARAS; D. W. C. MACMILLAN, *J. Am. Chem. Soc.* **2001**, 123, 4370.
- 19 Y. SUN OR; N. VO; J. WANG; L. T. PHAN (Enanta Pharm. Inc.) U.S. Patent 6,436,906, **2002**; Y. SUN OR; T. LAZAROVA; S. BINET; J. WANG; L. T. PHAN (Enanta Pharm. Inc.) U.S. Patent 6,440,942, **2002**; Y. SUN OR; T. LAZAROVA; S. BINET; J. WANG; L. T. PHAN (Enanta Pharm. Inc.) WO 02/060912 A1, **2002**.
- 20 D. SCHNIZER; A. LIMBERG; O. M. BOEHM; A. BAUER; M. CORDES (Novartis AG) US Patent 5,969,145, **1999**; D. SCHNIZER; A. LIMBERG; O. M. BOEHM; A. BAUER; M. CORDES (Novartis AG) US Patent 6,043,372, **2000**; D. SCHNIZER; A. LIMBERG; O. M. BOEHM; A. BAUER; M. CORDES (Novartis AG) US Patent 6,156,905, **2000**.
- 21 a) K. C. NICOLAOU; D. VOURLOUMIS; H. VALLBERG; F. ROSCHAMGER; F. SARABIA; S. NINKOVIC; Z. YANG; J. I. TRUJILLO, *J. Am. Chem. Soc.* **1997**, 119, 7960; b) Z. YANG; Y. HE; D. VOURLOUMIS; H. VALLBERG; K. C. NICOLAOU, *Angew. Chem. Intl. Ed. Engl.* **1997**, 36, 166; c) K. C. NICOLAOU; Y. HE; S. NINKOVIC; J. PASTOR; F. ROSCHAMGER; F. SARABIA; H. VALLBERG; D. VOURLOUMIS; N. WINSSINGER; Z. YANG; N. P. KING; M. R. FINLAY, US Patent 6,441,186 B1, **2002**; d) K. C. NICOLAOU, M. H. D. POSTEMA, E. W. YUE, A. NADIN, *J. Am. Chem. Soc.* **1996**, 118, 10335–10336; e) K. C. NICOLAOU, Y. HE, D. VOURLOUMIS, H. VALLBERG, Z. YANG, *Angew. Chem. Intl. Ed. Engl.* **1996**, 35, 2399–2401; f) K. C. NICOLAOU, N. P. KING, Y. HE, in *Vol. 1 Alkene Metathesis in Organic Synthesis*; A. FÜRSTNER, Vol. Ed. in *Topics in Organometallic Chemistry*, Springer-Verlag, New York, pp. 73–104, **1998**.
- 22 a) C. R. HARRIS; A. BALOG; K. SAVIN; S. J. DANISHEFSKY, *Actualités de Chemie Therapeutique* **1999**, 25, 187; b) S. J. DANISHEFSKY; A. BALOG; P. BERTINATO; D.-H. SU; T.-C. CHOA; D. MENG; T. KAMEDECKA; E. J. SORENSEN; S. KUDUK; C. HARRIS; X.-G. ZHANG; J. R. BERTINO (Sloan-Kettering Institute for Cancer Research, USA) WO 99/43653, **1999**; c) S. J. DANISHEFSKY; P. BERTINATO; D.-H. SU; D. MENG; T.-C. CHOU; T. KAMEDECKA; E. J. SORENSEN; A. BALOG; K. A. SAVIN; S. KUDUK; C. HARRIS; X.-G. ZHANG; J. R. BERTINO (Sloan-Kettering Institute for Cancer Research, USA) US Patent 6,204,388 B1, **2001**; d) S. J. DANISHEFSKY; P. BERTINATO; D.-H. SU; D. MENG; T.-C. CHOU; T. KAMEDECKA; E. J. SORENSEN; A. BALOG; K. A. SAVIN (Sloan-Kettering Institute for Cancer Research, USA) US Patent 6,300,355 B1, **2001**; e) S. J. DANISHEFSKY; P. BERTINATO; D.-H. SU; D. MENG; T.-C. CHOU; T. KAMEDECKA; E. J. SORENSEN; A. BALOG; K. A. SAVIN (Sloan-Kettering Institute for Cancer Research, USA) US Patent 6,316,630 B1, **2001**; f) F. MENG; D.-H. SU; A. BALOG; P. BERTINATO; E. J. SORENSEN; S. J. DANISHEFSKY; Y.-H. ZHENG; T.-C. CHOU; L. HE; S. B. HORWITZ, *J. Am. Chem. Soc.* **1997**, 119, 2733; g) P. BERTINATO; E. J. SORENSEN; D. MENG; S. J. DANISHEFSKY, *J. Org. Chem.* **1996**, 61, 8000.
- 23 G. APPENDINO; G. CASIRAGHI, *Chemtracts-Organic Chemistry*, **1998**, 11, 678–696, references therein.
- 24 K. BISWAS; H. LIN; J. T. NJARDARSON; M. D. CHAPPELL; T. C. CHOU; Y. GUAN; W. P. TONG; L. HE; S. B. HORWITZ; S. J. DANISHEFSKY, *J. Am. Chem. Soc.* **2002**, 124, 9825.
- 25 Kosan Biosciences Inc., November 20, 2002 press release, (www.kosan.com)

- 26 H. J. J. LOOZEN (Akzo Nobel N.V.) US. Patent 6,313,180, B1, **2001**.
- 27 R. E. OLSON (DuPont Pharmaceuticals Company) WO 01/92235 A1, **2001**.
- 28 R. E. OLSON (Bristol-Myers Squibb Com.) US **2002/0137737 A1, 2002**.
- 29 R. S. AL-AWAR; K. A. HECKER; J. HUANG; J. SAJAN; J. E. RAY (Eli Lilly and Company) WO 01/44235 A2, **2001**; R. S. AL-AWAR; K. A. HECKER; J. HUANG; J. SAJAN; J. E. RAY (Eli Lilly and Company) WO 01/44247 A2, **2001**.
- 30 R. W. MARQUIS; Y. RU; D. F. VERBER; M. D. CUMMINGS; S. K. THOMPSON; D. S. YAMASHITA (Smithkline Beecham Corp.) WO 00/38687, **2000**; R. W. MARQUIS; Y. RU; D. F. VERBER; M. D. CUMMINGS; S. K. THOMPSON; D. S. YAMASHITA (GlaxoSmithkline Corp.) US **2002/01477188 A1, 2002**; R. W. MARQUIS; D. F. VERBER (Smithkline Beecham Corp.) WO 00/49011, **2000**. R. W. MARQUIS; D. F. VERBER (Smithkline Beecham Corp.) WO 01/95911, **2001**.
- 31 S. E. RUSSO-RODRIGUEZ; K. KOCH; A. TERMIN; C. HUMMEL (Amgen, Inc.) US 6,107,291, **2000**; K. KOCK; A. TERMIN; J. A. JOSEY (Amgen, Inc.) US 6,291,450 B1, **2001**; K. KOCK; A. TERMIN; J. A. JOSEY (Amgen, Inc.) US 6,335,329 B1, **2002**; K. KOCK; A. TERMIN; J. A. JOSEY (Amgen, Inc.) US **2002/0065269 A1, 2002**; S. E. RUSSO-RODRIGUEZ; K. KOCH; A. TERMIN; C. HUMMEL (Amgen, Inc.) WO 99/32451 **1999**; K. KOCK; A. TERMIN; J. A. JOSEY (Amgen, Inc.) WO 99/32452, **1999**.
- 32 a) P. R. HANSON; K. T. SPROTT; M. D. McREYNOLDS (University of Kansas) WO 02/4344, **2002**; b) M. D. McREYNOLDS; K. T. SPROTT; P. R. HANSON, *Org. Lett.* **2002**, *4*, 4673; c) K. T. SPROTT; M. D. McREYNOLDS; P. R. HANSON, *Synthesis* **2001**, *4*, 612; d) K. T. SPROTT; P. R. HANSON, *J. Org. Chem.* **2000**, *65*, 7913.
- 33 a) J. M. DOUGHERTY; D. A. PROBST; R. E. ROBINSON; J. D. MOORE; T. A. KLEIN; K. A. SNELGROVE; P. R. HANSON, *Tetrahedron* **2000**, *56*, 9781; b) P. R. HANSON; D. A. PROBST; R. E. ROBINSON; M. YAU, *Tetrahedron Lett.* **1999**, *40*, 4767.
- 34 J. D. MOORE; K. T. SPROTT; P. R. HANSON, *J. Org. Chem.* **2002**, *67*, 8123.
- 35 D. S. STOIANOVA; P. D. HANSON, *Org. Lett.* **2000**, *2*, 1769; K. T. SPROTT; M. D. McREYNOLDS; P. R. HANSON, *Synthesis* **2001**, *4*, 3939.
- 36 P. R. HANSON; J. M. DOUGHERTY; D. A. PROBST (University of Kansas) WO 02/14287, **2002**.
- 37 G. D. CUNY; J. CAO; J. R. HAUSKE, US Patent 6,486,324 B2, **2002**; G. D. CUNY; J. CAO; J. R. HAUSKE, US Patent 6,177,464 B1, **2001**; G. D. CUNY; J. CAO; J. R. HAUSKE, US **2002/0042406 A1, 2002**; G. D. CUNY; J. CAO; J. R. HAUSKE, US **2001/0034341 A1, 2001**; G. D. CUNY; J. CAO; J. R. HAUSKE, WO 98/40373, **1998**.
- 38 A. G. M. BARRETT; M. AHMED; S. P. BAKER; S. P. D. BAUGH; D. C. BRADDOCK; P. A. PROCOPIOU; A. J. P. WHITE; D. J. WILLIAMS, *J. Org. Chem.* **2000**, *65*, 3716.
- 39 D. J. WALLACE; J. M. GOODMAN; D. J. KENNEDY, JR.; A. J. DAVIES; C. J. COWDEN; M. S. ASHWOOD; I. F. COTTRELL; U.-H. DOLLING; P. J. REIDER, *Org. Lett.* **2001**, *3*, 671; D. J. WALLACE; C. J. COWDEN; D. J. KENNEDY, JR.; M. S. ASHWOOD; I. F. COTTRELL; U.-H. DOLLING, *Tetra. Lett.* **2000**, *41*, 2027.
- 40 S. LIRAS; J. E. DAVOREN; J. BORDNER, *Org. Lett.* **2001**, *3*, 703.
- 41 S. LIRAS; M. P. ALLEN; J. F. BLAKE, *Org. Lett.* **2001**, *3*, 3483.
- 42 R. C. D. BROWN; J. L. CASTRO; J.-D. MORIGGI, *Tetra. Lett.* **2000**, *41*, 3681.
- 43 P. Y. LAM; P. K. JADHAV; C. J. EYERMANN; C. N. HODGE; G. V. DE LUCCA; J. D. ROBERTS, US 5,610,294, **1997**.
- 44 A. L. HANDLON; G. L. HODGSON; C. E. HYMAN; E. CLIFTON, WO 98/38182, **1998**.
- 45 K. MAKINO; T. SATO; K. MORIMOTO; S. AKIYAMA; H. SUZUKI; K. SUZUKI; T. NAWAMAKI; S. WATANABE, EP Patent 342456, **1998**.
- 46 D. D. LONG; A. P. TERMIN, *Tetra. Lett.* **2000**, *41*, 6743.
- 47 a) D. LABRECQUE; S. CHARON; R. REJ; C. BLAIS; S. LAMOTHE, *Tetra. Letters*, **2001**, 2645; b) Y. WU; L. ESSER; J. K.

- DE BRABANDER, *Angew. Chem. Int. Ed.* **2000**, 39, 4308; c) Y. WU; J. K. DE BRABANDER, *Org. Lett.* **2000**, 2, 4241; d) G. I. GEORG; B. BLACKMAN; C. J. MOSSMAN; K. YANG; P. T. FLAHERTY, Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26–30, **2000**, ORGN-808; e) A. FUERSTNER; O. R. THIEL; G. BLANDA, *Org. Lett.* **2000**, 2, 3713; f) B. B. SNIDER; F. SONG, *Org. Lett.* **2000**, 2, 407; g) K. KURAMOCHI; H. WATANABE; T. KITAHARA, *Synlett* **2000**, 397; h) R. SHEN; J. A. PORCO, JR., *Org. Lett.* **2000**, 2, 1333; h) J. T. FUETRILL; G. A. HOLLOWAY; F. HILL; H. M. HUGEL; M. A. RIZZACASA, *Tetrahedron Lett.* **2000**, 41, 8569.
- 48 M. D. WATSON; K. B. WAGENER, *Macromolecules* **2000**, 33, 3196.
- 49 A. E. SUTTON; B. A. SEIGAL; D. F. FINNEGAN; M. C. SNAPPER, *J. Am. Chem. Soc.* **2002**, 124, 13390.
- 50 S. J. DANISHEFSKY; M. T. BILDOEAU, *Angew. Chem. Intl. Ed. Engl.* **1996**, 35, 1380.
- 51 J. S. CLARK; J. G. KETTLE, *Tetrahedron* **1999**, 55, 8231; T. L. B. BOIVIN, *Tetrahedron* **1987**, 43, 3309.
- 52 P. MAGNUS; M. B. ROE, *Tetrahedron Lett.* **1996**, 37, 303.
- 53 J. LOUIE; C. W. BIELAWSKI; R. H. GRUBBS, *J. Am. Chem. Soc.* **2001**, 123, 11312.
- 54 C. W. BIELAWSKI; J. LOUIE; R. H. GRUBBS, *J. Am. Chem. Soc.* **2000**, 122, 12872.
- 55 J. J. VAN VELDHIJZEN; S. B. GARBER; J. S. KINGSBURY AND A. H. HOVEYDA, *J. Am. Chem. Soc.* **2002**, 124, 4954.
- 56 T. J. SEIDERS, D. W. WARD, R. H. GRUBBS, *Org. Lett.* **2001**, 3, 3225.

3.1

Introduction

Robert H. Grubbs

Olefin metathesis was discovered while examining the polymerization of olefins. It is only appropriate that this area drove the early days of development of metathesis using well-defined catalysts. To the best of my knowledge, the term ROMP to describe metathesis polymerization was first used by Tim Swager, when he was a graduate student in my laboratory at Caltech. Chapters have been chosen that start with a short history of the early catalysts, move to the discovery of “living ROMP,” which marks the start of the modern developments, and ends with present commercial applications of the well-defined catalysts in the synthesis of commercial products. The central sections discuss applications from the practical synthesis of support materials for catalysts and separations to the design of materials to probe the surface of cells. A short section on ROMP gels was included with combinatorial applications in the organic section.

3.2

Living Ring-Opening Olefin Metathesis Polymerization

Gráinne Black, Declan Maher, and Wilhelm Risse

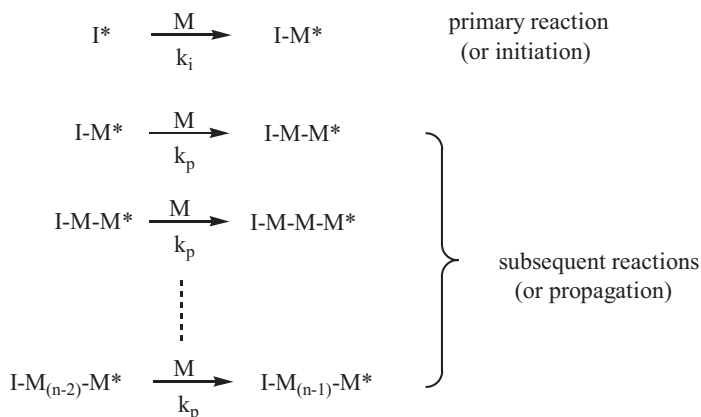
3.2.1

Historic Overview of Living Polymerization Systems

The terms “living polymerization” and “living polymer” were introduced by Szwarc following his groundbreaking work on anionic polymerizations in 1956 [1]. He stated that macromolecules synthesized in chain polymerization reactions are “born” through an initiation process, “grow” by a propagation process, and “die” as a result of a termination process. The average molecular weight and the molecular weight distribution are controlled by the experimental conditions. When no termination occurs, the polymer molecules “live” for an indefinite period of time. However, a living polymer chain does not grow indefinitely. As Szwarc outlined, “food” is required for growth to occur, and small monomer molecules such as styrene represent the “food” in living polymerization reactions. Macromolecular chain growth is suspended once all of the small molecules are consumed. When an additional amount of monomer is added to the reaction mixture, the living chain ends resume polymer chain growth.

As early as 1928, Ziegler had begun to recognize the main principles of living polymerizations. His group investigated reactions of the monomers styrene, butadiene, and alky-substituted butadienes with main group organometallic compounds such as 2-phenylisopropyl potassium (1-methyl-1-phenylethyl potassium) [2]. When the initial reaction mixture contained an excess amount of the olefin, several successive olefin additions occurred. The product molecular mass was directly proportional to the mole ratio of olefin to organometallic reagent. This indicated that the reactivity of the intermediates formed during each reaction step was similar to that of the initiating alkyl potassium compound.

In styrene polymerizations, the reaction mixtures retained their characteristic red color after all monomer molecules had been consumed, which demonstrated that the reactive sites responsible for chain growth remained intact. Ziegler concluded that the synthesis of very large molecules was possible by reacting large quantities of olefin with a small amount of organometallic initiator. He also pointed out that the rates of the primary reaction, i.e., the reaction between initia-



$\text{I}^* = 1\text{-methyl-1-phenylethyl potassium or triphenylmethyl sodium}$

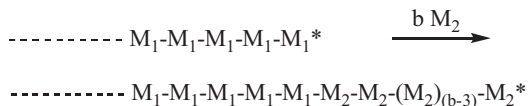
$\text{M} = \text{styrene- or butadiene- or methyl-substituted butadienes}$

Control of molecular mass requires k_i larger or similar to k_p

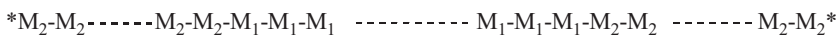
Scheme 3.2-1. Initiation and propagation in chain polymerizations of monomers (M).

tor and monomer (rate constant k_i in Scheme 3.2-1), and subsequent propagation steps (rate constant k_p in Scheme 3.2-1) need to be similar if the product molar mass is to be controlled by the initial mole ratio of olefin to initiator [2c].

In the following decades, other groups established an anionic polymerization mechanism [3] for the oligomerization and polymerization reactions investigated by Ziegler. Szwarc et al. [1] used naphthalene sodium [4] as an initiator, and they demonstrated that polymer chain growth continued when more monomer was added to the reaction mixture after the initial amount of styrene had reacted. Resumption of polymer chain growth led to a significant increase in the solution viscosity. The addition of a different monomer such as isoprene to the living polystyrene species resulted in the formation of block copolymer structures in which polymer segments composed of polystyrene and polyisoprene sequences were linked by covalent bonds (Scheme 3.2-2) [1, 5]. The molecular mass of these



or



triblock copolymers via anionic polymerization with naphthalene sodium

Scheme 3.2-2. Block copolymer synthesis employing two monomers M_1 and M_2 .

products could be controlled by the quantity of monomer consumed and the amount of initiator employed. The polymers displayed very narrow molecular weight distributions.

It is important to note that the highly reactive and unselective nature of the anionic chain ends requires stringent control of the reaction conditions, such as strict absence of moisture and air, in order to achieve exact control of the polymer molecular mass and mass distribution. The use of thoroughly purified reagents and solvents is essential for these anionic vinyl-type polymerizations to proceed without termination. Only a limited number of olefin monomers can be polymerized in a controlled fashion, as the carbanionic end groups of the growing polymer chains readily react with a large number of functional groups and chain propagation is thereby terminated [6].

Over the last two decades, there has been considerable progress in optimizing chain polymerization methodologies [7], and controlled polymerizations via cationic [8], radical [9], migratory insertion [10], and, in particular, olefin metathesis polymerization [11] are now possible. This has increased the range of monomers that can undergo living polymerization. The absence of chain termination and chain transfer are very important features of controlled polymer chain growth that allow access to well-defined macromolecular architectures such as block copolymer and comb- and star-shaped polymer structures (Scheme 3.2-3) [6a, 7c, 12].

Well-defined structures may find future use as highly valuable materials for advanced microelectronic and biomedical applications. Current studies of interest include the development of porogens with controlled size distribution for low dielectric materials [13], the synthesis of macromolecular drug-delivery vehicles [14], and the design of biodegradable medical devices that display shape-memory effects [15].

3.2.2

Definition of Living Polymerization and Relevant Terminology

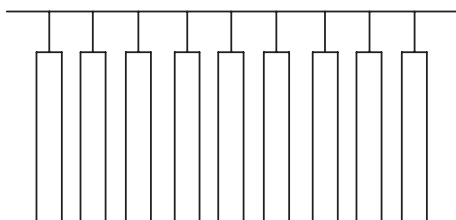
There are two general categories of polymerization reactions: chain and step polymerizations [16]. Living polymerization is a special case of chain-growth polymerization. The current IUPAC definition [17] states that a living polymerization is a chain polymerization from which chain-transfer and chain-termination reactions are absent. In many cases, the rate of chain initiation is fast compared with the rate of chain propagation, so that the number of kinetic chain carriers is essentially constant throughout the polymerization and macromolecules of uniform length are obtained.

Essential criteria for an ideal living polymerization are:

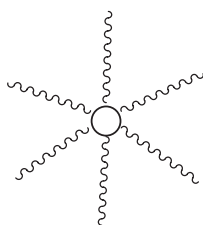
- Complete and rapid initiation: The initiator reacts with monomer, and a polymerization-active species is created. The rate of initiation needs to be similar to or preferably greater than the rate of propagation. In this way, the initiator is



$(AB)_n$ -type multiblock copolymer



comb-shaped polymer



star-shaped polymer

Scheme 3.2-3. Macromolecular architectures.

consumed in the early stages of polymerization, and each polymer chain starts to grow at approximately the same time.

- Irreversible propagation steps: The monomer must add irreversibly in order for a polymerization to proceed in a living manner.
- Absence of chain termination and chain transfer: The active chain ends or active sites responsible for chain propagation do not undergo chain termination or chain transfer. This means that they do not become detached from the growing polymer chains, and they do not undergo any inadvertent decomposition or secondary reactions with solvent, monomer, or other polymer molecules. Polymerization proceeds to complete monomer conversion, and the active sites remain intact after all monomer molecules have been consumed. Polymer growth continues upon subsequent monomer addition. A second monomer can be added after the first monomer has been completely consumed, producing AB- and ABA-type block copolymers containing blocks of uniform length.

Characteristics of a living system are:

- Linear dependence of number-average molecular weight on monomer conversion: The polymer molecular weight M_n increases in a linear fashion with percentage monomer conversion.
- Control of molecular weight and narrow molecular weight distributions: The final molecular weights can be precisely controlled through the stoichiometry employed, and the polymer products display narrow molecular weight distributions. The molecular weight distribution is quantified in terms of the polydispersity index (PDI), which is the ratio of weight-average, M_w , and number-average, M_n , molecular weights M_w/M_n [18]. Living systems are usually characterized by a PDI between 1.0 and 1.1. In ideal living polymerizations, each event leading to chain growth is equally probable, and the polymerization system can be statistically described in terms of a Poisson distribution [19]. (The theoretical polydispersity index of such a distribution is $M_w/M_n = 1 + 1/P_n$, with P_n representing the average degree of polymerization).

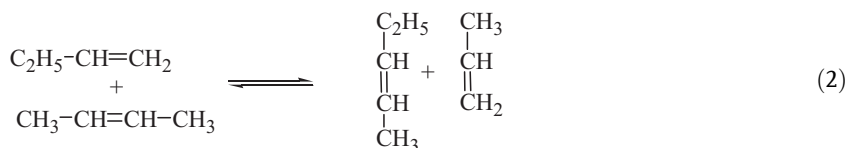
3.2.3

Introduction to ROMP

Ziegler and Natta's landmark discoveries of ethylene and propylene polymerizations [20, 21] initiated intense research efforts on transition-metal-catalyzed olefin polymerizations and the reaction mechanisms involved. These activities led to the discovery of ring-opening olefin metathesis polymerization (ROMP) [22], which has subsequently become an important reaction for the polymer chemist [23]. Transition metal catalysts opened up new, unexpected ways of polymerizing monocyclic, bicyclic, and polycyclic olefins. The overall reaction involves breaking and reforming olefin double bonds with simultaneous opening of the unsaturated cycles of the monomers [24–26]. Thus, the total amount of unsaturation is retained, and the resulting polymers are comprised of repeating units that contain carbon-carbon double bonds (Eq. (1)). Common examples of cyclic olefin monomers include cyclobutene, cyclopentene, cyclooctene, norbornene, and dicyclopentadiene [23]. The release of ring strain [27] provides the main driving force that is required to overcome the unfavorable entropy change in polymerization [16, 28]. Accordingly, low-strained cyclohexene is difficult to polymerize [29], and norbornene with a released ring strain of more than 15 kcal mol⁻¹ undergoes reaction readily with a large number of metathesis catalysts.



Banks and Bailey discovered disproportionation of acyclic olefins (Eq. (2)) in independent work [30], which Calderon et al. subsequently found to involve olefin metathesis [24], the same type of reaction as ROMP.



A wide range of catalyst compositions based on the transition elements Ti, V, Nb, Ta, Cr, Mo, W, Re, Co, Ir, Ru, and Os are active for ROMP [11, 31]. However, the predominant fractions of these are conventional two- and three-component catalyst mixtures of undefined structure that were developed during the first two decades of olefin metathesis chemistry (from the early 1960s to the early 1980s). Examples of supported and unsupported catalysts include $\text{MoO}_3/\gamma\text{-Al}_2\text{O}_3/\text{LiAlH}_4$ [22b], $\text{MoCl}_5/\text{Et}_3\text{Al}$ [32], $\text{TiCl}_4/\text{Et}_3\text{Al}$ [33], $\text{TiCl}_4/\text{LiAl}(n\text{-C}_7\text{H}_{15})_4$ [22c], $\text{WCl}_6/\text{EtAlCl}_2/\text{EtOH}$ [24], $\text{MoCl}_2(\text{NO})_2\text{L}_2/\text{EtAlCl}_2$, (L = phosphine or py) [34], $\text{WCl}_6/(\text{C}_2\text{H}_5)_4\text{Sn}$ [35], $\text{WOCl}_4/(n\text{-C}_4\text{H}_9)_4\text{Sn}$ [36], $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ [37], and RuCl_3 in polar solvent media [38]. These conventional catalysts do not facilitate polymerization in a well-controlled manner and therefore do not produce living polymers. They are often affected by one or more of the following limitations: (1) the formation of several transition metal species, some of which are not metathesis active; (2) slow generation of the active catalytic species relative to the rate of chain propagation; (3) the existence of several propagating species that promote polymer chain growth independently of each other at different rates of polymerization; (4) chain-transfer steps such as backbiting; and (5) termination steps.

Detailed investigations of the catalytic mechanism established that transition metal carbenes and metallacyclobutanes represent key intermediates in olefin metathesis [11, 31, 36]. Carbene complexes with metals in a high oxidation state are also called transition metal alkylidenes [39]. Several academic and industrial laboratories made significant contributions towards elucidating the reaction mechanism during the 1960s, 1970s, and 1980s. These involved the use of cyclic and acyclic alkenes, and prominent examples are summarized below.

Calderon et al. at Goodyear [24] carried out cross-metathesis reactions of equimolar mixtures of 2-butene and 2-butene- d_8 and found that the reaction proceeded by cleaving alkene double bonds, rather than involving C–C single bonds as initially proposed.

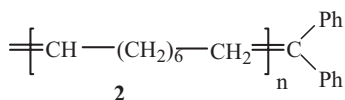
Chauvin et al. [36] performed tungsten-catalyzed cross-metathesis reactions between cyclopentene and 2-pentene and obtained the resulting three diolefin products in the thermodynamically favored ratio of 1:2:1 after very short reaction times. They proposed that transition metal-carbene complexes containing the structural unit W=CHR are the catalytically active species [36]. This was subsequently confirmed by several independent studies involving isotope labeling, kinetics, and crossover experiments and by using single-component transition metal-carbene complexes.

Grubbs et al. and Katz et al. [40] carried out elegant ring-closing metathesis/crossover studies using equimolar mixtures of 1,7-octadiene/1,1,7,7-tetradeuterio-1,7-octadiene and 2,2'-divinylbiphenyl/2,2'-divinylbenzene- d_4 (with the terminal

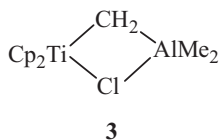
olefin carbons bearing the four deuterium labels), respectively. The product distribution of deuterated and non-deuterated ethylenes $\text{CH}_2=\text{CH}_2$, $\text{CH}_2=\text{CD}_2$, $\text{CD}_2=\text{CD}_2$ recorded after very short reaction times is in agreement with a metal-carbene-based mechanism [40].

Fischer et al. and Casey et al. prepared metal complexes $(\text{CO})_5\text{Cr}=\text{C}(\text{OMe})\text{Ph}$ and $(\text{CO})_5\text{W}=\text{CAr}_2$ (with $\text{Ar} = \text{Ph}$, **1**, or 4- CH_3 -Ph), respectively [41a,b]. They observed that alkylidene fragments of olefins and these transition metal carbenes could be interchanged [41c–e]. The product olefins were formed from the $=\text{CHR}$ fragments ($\text{R} = \text{H}$ or alkyl) of the alkene reagent and the carbene units of the transition metal complex. Casey invoked an olefin metathesis mechanism [41e] similar to that proposed by Chauvin et al. [36].

Katz et al. catalyzed nonliving metathesis polymerization of cyclooctene with Casey's carbene $(\text{CO})_5\text{W}=\text{CPh}_2$, **1**, and found that Ph_2C units from **1** had become attached to the polymer chain ends of the ring-opened cyclooctene polymer **2** [42].

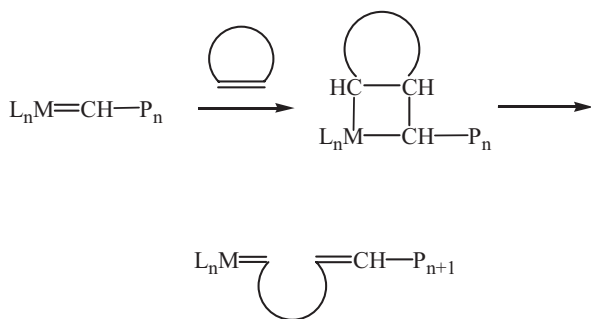


Bimetallic methylidene compound **3** described by Tebbe et al. [43] can be regarded as a well-defined Ti carbene that is stabilized by coordination of Me_2AlCl . This Ti complex catalyzes the exchange of labeled and unlabeled methylene units between $^{13}\text{CH}_2=\text{CMe}_2$ and methylenecyclohexane via nonproductive metathesis. Catalyst **3** (partially ^{13}C -labeled) is re-isolated in high yield at the end of the reaction [43].



A series of tantalum and niobium alkylidene complexes was prepared by Schrock et al. They found that $\text{Ta}(=\text{CHCMe}_3)(\text{THF})_2\text{Cl}_2$ and $\text{Nb}(=\text{CHCMe}_3)(\text{OCMe}_3)_2(\text{PMe}_3)\text{Cl}$ were the first well-defined isolable alkylidene complexes that successfully catalyzed productive metathesis of internal alkenes [44]. Decomposition pathways and rearrangement reactions were retarded, and several equivalents of *cis*-2-pentene were converted to 2-butene and 3-hexene before these catalysts became deactivated.

An early example of a tungsten-alkylidene complex synthesized by Schrock et al., $\text{W}(\text{O})(=\text{CHCMe}_3)(\text{PEt}_3)_2\text{Cl}_2$ [45], was found to catalyze olefin metathesis of 1-butene when activated by a Lewis acid such as AlCl_3 . Alkylidene complexes $[\text{W}]=\text{CH}_2$ and $[\text{W}]=\text{CHC}_2\text{H}_5$ (with $[\text{W}]$ corresponding to $\text{W}(\text{O})(\text{PEt}_3)_2\text{Cl}_2$) were isolated and identified as the reactive intermediates.

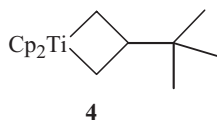


Scheme 3.2-4. Chain propagation in ROMP.

Similar alkylidene complexes were subsequently detected by Osborn et al. in a low-temperature ^1H NMR study on olefin metathesis of *cis*-2-pentene with mixtures of $\text{W}(=\text{CHCMe}_3)(\text{OCH}_2\text{CMe}_3)_2\text{Br}_2$ and AlBr_3 [46].

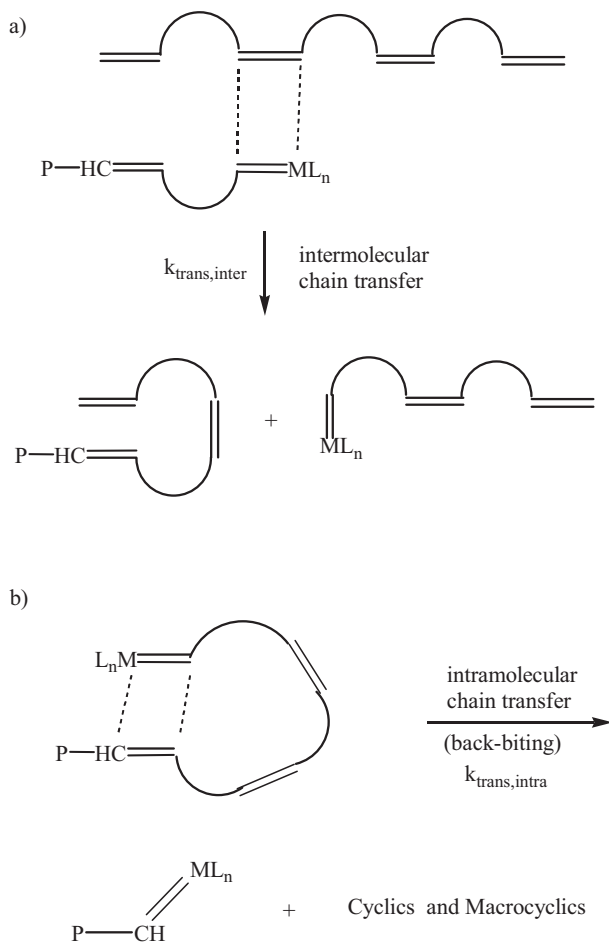
Ivin, Rooney, and coworkers thoroughly investigated metathesis polymerizations of a large number of norbornene derivatives catalyzed by conventional systems. They advanced structural analysis of polynorbornenes by ^{13}C NMR spectroscopy, and they proposed early models for relating the polymer microstructure to the mechanism of polymerization [31a, 47]. These studies were complemented by the early work of Feast et al., who investigated metathesis polymerizations of fluoro-substituted norbornene derivatives [48].

Grubbs et al. isolated titanacyclobutane compounds such as **4** from reactions of Tebbe reagent **3** with olefins and found that they catalyzed metathesis reactions [31b, 49]. This reaction sequence represents experimental proof that metallacyclobutanes are intermediates in olefin metathesis, as previously suggested by Casey et al. and Chauvin et al. Accordingly, chain propagation in ROMP can be described as a reaction that proceeds via interconversion of metal carbenes and metallacyclobutanes (Scheme 3.2-4).



These fundamental results were important steps on the path to the design of well-defined catalysts for living ROMP. Potential catalyst deactivation reactions such as bimolecular decomposition of carbenes [50] or metallacycle rearrangements via β -H migration [51] had to be avoided because they would terminate polymer chain propagation. The design of single-component, structurally uniform metallacyclobutanes and transition metal carbenes with bulky and chemically inert ligand spheres was key to arriving at living polymerizations via ROMP.

It was also essential that secondary metathesis of olefin units within the growing polymer chains was either completely inhibited or very significantly retarded. This



Scheme 3.2-5. Secondary metathesis reactions, such as a) intermolecular and b) intramolecular chain transfer, which are not desired in living ROMP.

reaction pathway would either lead to transfer of the (polymerization-active) transition metal units to other macromolecules in the reaction mixture (chain transfer) or produce macrocycles via intramolecular “backbiting” (Scheme 3.2-5) [31a, 52]. These reactions prevent polymerization from proceeding in a living fashion. Deactivation of some of the polymer chains would occur and lead to broadening of the molecular weight distributions. The catalyst activity needed to be elegantly fine-tuned to guarantee that the rate constants for chain transfer $k_{\text{trans,inter}}$ and $k_{\text{trans,intra}}$ were negligible compared to the rate constant for chain propagation.

Highly strained cyclobutene and norbornene are ideally suited for living ROMP. These cyclic olefins and their derivatives display ring strains of more than 15 kcal mol⁻¹ [27]. They are substantially more reactive toward olefin metathesis than

the olefin units in the resulting polymer chains, and catalysts with optimized metathesis activity can selectively react with the cyclic olefin double bonds.



In addition to the absence of chain-termination and chain-transfer processes, fast and efficient conversion of the well-defined ROMP catalyst into propagating polymer chains is important for control of polymer molecular mass and for producing narrow molecular mass distributions.

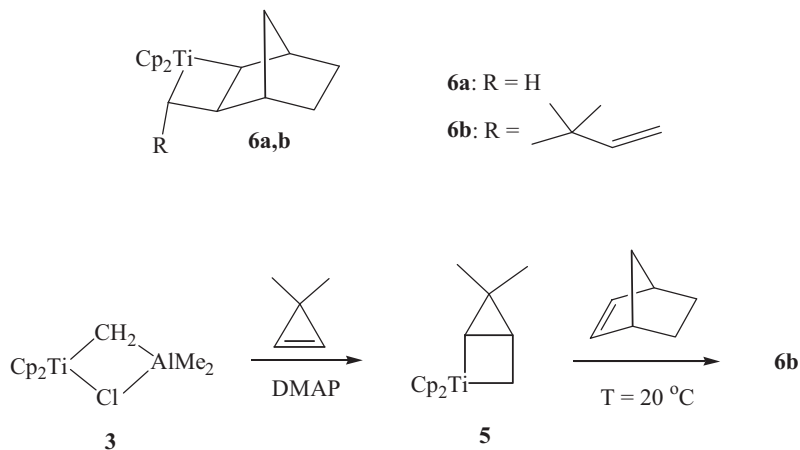
3.2.4 Olefin Metathesis Catalysts for Living Polymerizations

3.2.4.1

Titanacyclobutane Compounds

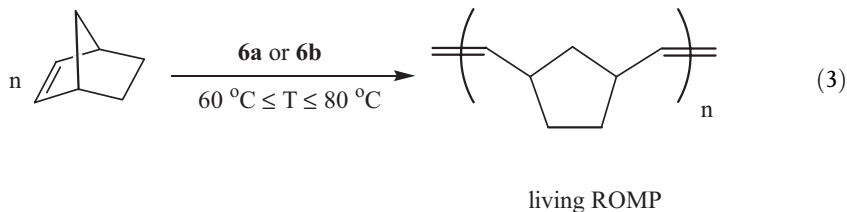
Bis(cyclopentadienyl)titanacyclobutane compounds **6a** and **6b**, developed by Grubbs and Gilliom [53], were the first well-defined metathesis catalysts found to carry out polymerizations that satisfy all the definitive criteria of a living system [53b,c]. These titanium compounds can be prepared from the Tebbe reagent **3**. A two-step reaction sequence for the preparation of complex **6b** is displayed in Scheme 3.2-6. The synthesis involves reaction of bimetallic complex **3** with 3,3-dimethylcyclopropene to give titanacyclobutane **5**. Complex **5** is subsequently converted to catalyst **6b** via reaction with 1 equivalent of norbornene at 20 °C.

Both titanacyclobutanes **6a** and **6b** are moderately active for olefin metathesis, and they catalyze the polymerization of norbornene upon heating to temperatures

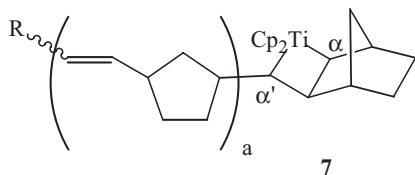


Scheme 3.2-6. Synthesis of titanacyclobutane complex **6b**.

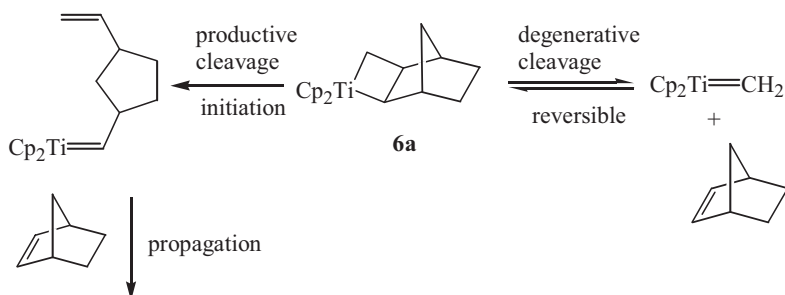
above 60 °C (Eq. (3)). Polymerization proceeds in a well-controlled manner without termination or chain transfer [53b]. The polymer products display narrow and controllable molecular weight distributions. A plot of M_n vs. monomer conversion is linear with a zero intercept, and the final molecular mass is determined by the ratio of the number of equivalents of monomer consumed per titanacycle.



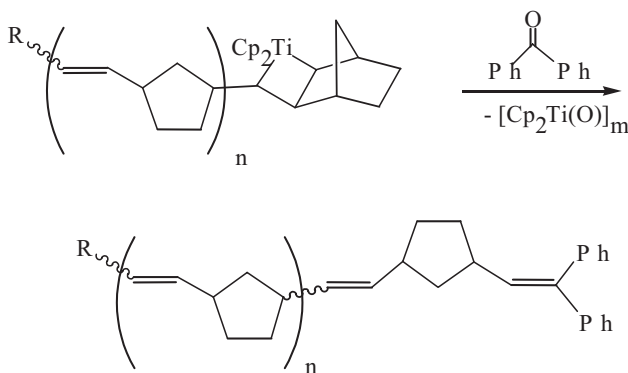
^1H NMR analysis reveals that the species responsible for polymer chain growth are structurally well defined: they are α,β,α' -trisubstituted metallacyclobutanes **7** that remain attached to the ends of the growing polymer chains. These titanacyclobutane intermediates are formed when norbornene and catalyst are reacted at a temperature between 60 °C and 80 °C. Characteristic ^1H NMR signals are detected at δ 3.67 (doublet) and -0.22 ppm (multiplet) that correspond to the α and β protons of the titanacycle in **7**. The intensity of these signals increases at the beginning of the polymerization, and simultaneously the ^1H NMR signals assigned to the initiating catalyst species **6a** or **6b** become weaker [53b]. Metallacycle **6b** is completely converted into chain-propagating titanacycle **7** within a few minutes after the start of the reaction, and thereafter the signal intensity for the metallacycle in **7** remains constant and does not become diminished as long as monomer molecules are present. This indicates that the number of growing polymer chains does not change.



Chain propagation reversibly stops upon cooling the polymerization mixture to 0 °C with no decrease in ^1H NMR signal intensity for the titanacyclobutane unit. Polynorbornene samples containing the active metallacycle end group can be isolated by removing solvent and unreacted monomer (by applying vacuum). The living polymer retains its activity for more than 3 months when stored under an inert gas atmosphere. The polymerization resumes upon heating in the presence of additional monomer. Each polymer chain remains active until the reaction is terminated by added reagent such as benzophenone. This further confirms the



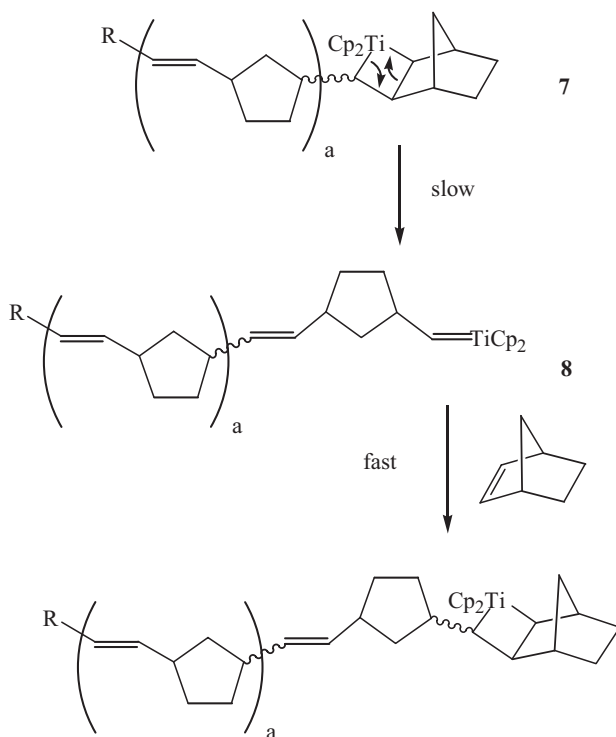
Scheme 3.2-7. Slightly retarded initiation with titanacycle **6a**.



Scheme 3.2-8. End-capping of titanacyclobutanes via Wittig-type chemistry.

living nature of the polymerization, as does the molecular mass analysis of isolated polynorbornene samples. The chain-propagating end groups in polymerizations with **6a** and **6b** are identical; however, the rate of initiation is lower for catalyst **6a**, as it cleaves in both a productive and a reversibly degenerative manner (Scheme 3.2-7) [53b]. Slower initiation leads to slightly broader molecular mass distributions for polynorbornene samples prepared with ROMP catalyst **6a**. Thus, a polymer prepared from titanacycle **6a** and 100 equivalents of norbornene displays a polydispersity index M_w/M_n of 1.13 compared to M_w/M_n of 1.08 for a sample obtained from **6b** and the same amount of monomer. Backbiting and secondary isomerization reactions are not observed. Conventional ROMP catalyst systems previously used did not allow precise control over the molar mass.

Kinetic analysis [53b] and Wittig-type reactions [54] of the chain-growing intermediates with ketones (Scheme 3.2-8) provided an interesting insight into the mechanism of polymerization. Chain propagation involves rate-determining cleavage of the titanacycle unit of **7** via a retro [2+2] cycloaddition mechanism. This cleavage occurs in a productive fashion and produces the highly reactive titanium-carbene species of **8** (Scheme 3.2-9). Compound **8** is rapidly trapped via reaction

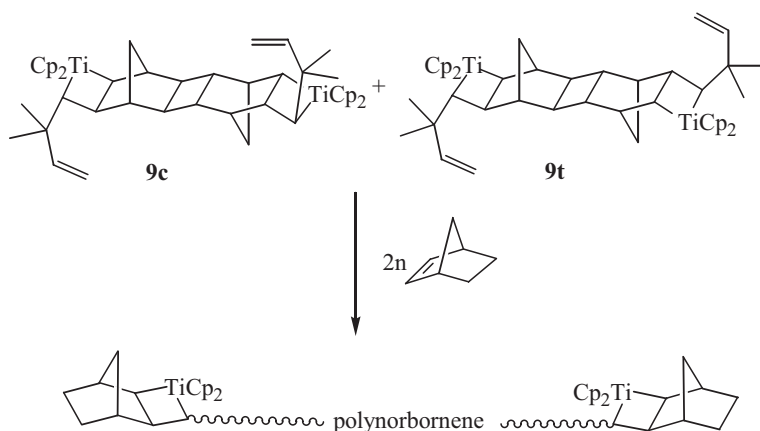


$\text{R} = \text{H} \text{ or } -\text{C}(\text{Me})_2\text{-CH=CH}_2$

Scheme 3.2-9. Chain propagation in titanacyclobutane-catalyzed ROMP.

with norbornene and reforms a titanacyclobutane. The polynorbornene chain is thereby extended by one repeating unit after each catalytic cycle. The rate of polymerization is first order in catalyst concentration and independent of the concentration of monomer. This is consistent with rate-determining unimolecular cleavage of the titanacycle end group of 7. Further evidence for rate-determining metallacycle cleavage is provided by the positive entropy of activation of $\Delta S^\ddagger = 9$ (+4) e.u. A zero-order monomer dependence allows polymerization to any desired molecular mass by adjusting the reaction time.

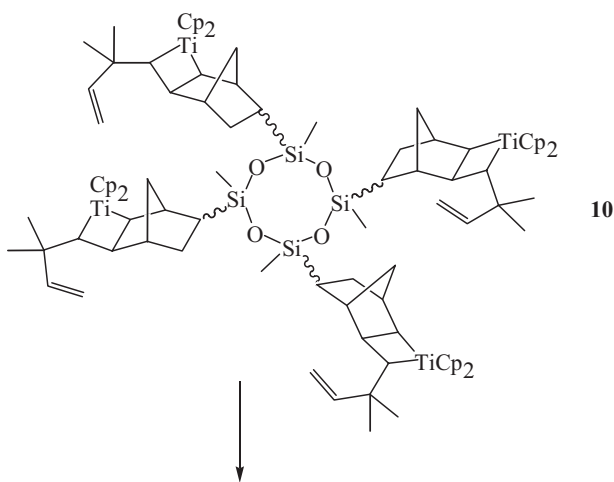
Consecutive metathesis polymerization of two different monomers affords block copolymers [55]. Similar to the first living polymerization systems pioneered by Ziegler et al. and Szwarc et al., ROMP polymerizations with titanacyclobutane catalysts are highly sensitive to moisture. Neither do these titanium-based ROMP systems tolerate the presence of most functionalities including aldehyde, ketone, ester, and hydroxyl groups. This lack of selectivity limits titanacyclobutane-catalyzed ROMP to the use of pure hydrocarbon-based cyclic olefins that display a significant amount of ring strain, and polymerization is carried out using non-protic solvents under an inert gas atmosphere.



Scheme 3.2-10. Bifunctional titanacycle initiators for polymer chain growth in two directions.

Wittig-type chemistry of the reactive titanacyclobutane end groups allows coupling of these living polymers with other polymer blocks that contain ketone groups. These reactions lead to the formation of block and graft copolymer structures [56]. Similarly, Wittig-type reactions can be used for switching from living ROMP to aldol group transfer polymerization. An aldehyde group is the polymerization-active unit in the latter polymerization method [57].

Bis(titanacyclobutane) catalyst **9c,t** can be employed for simultaneous polymer chain growth in two directions and allows the synthesis of polynorbornene that contains two reactive titanacyclobutane end groups (Scheme 3.2-10). In a similar manner, tetrakis(titanacyclobutane) compound **10** catalyzes ring-opening polymerization in four directions. This compound was used in early studies on the synthesis of star-shaped ROMP products [58].

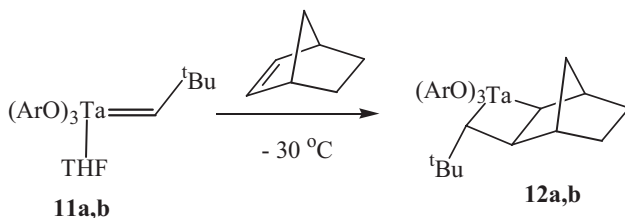


3.2.4.2

Tantalum-Alkylidene and Tantalacyclobutane Complexes for Norbornene Polymerizations

In subsequent years, the principles of living ROMP were successfully extended to a series of well-defined complexes that contain other transition metals. Schrock et al. [11c,f] reported several structurally uniform Ta, Mo, and W catalysts that catalyze living ROMP. First, the focus will be on two Ta-based catalytic systems that result in living or close to living polymerizations.

Tantalacyclobutane compounds **12a,b** can be prepared from tantalum alkylidenes **11a,b** and 1 equivalent of norbornene at $-30\text{ }^{\circ}\text{C}$. Both complexes **12a** and **12b** polymerize norbornene at temperatures between $35\text{ }^{\circ}\text{C}$ and $70\text{ }^{\circ}\text{C}$ [59]. Polymer chain growth catalyzed by the 2,6-diisopropylphenoxide-based tantalacycle **12a** occurs in a similar fashion to the polymerizations initiated by titanacyclobutanes **6a** and **6b**. Chain propagation proceeds when the polymerization mixture is kept at an elevated temperature and reversibly stops when cooled to $25\text{ }^{\circ}\text{C}$ or below. The rate of reaction is first order in tantalum compound **12a** and does not depend on the concentration of norbornene [59]. As observed for norbornene polymerizations with titanacyclobutanes, ring-opening of the metallacycle is the rate-determining step, and similar activation parameters were determined: $\Delta H^{\ddagger} = 24.0$ (0.9) kcal mol^{-1} , $\Delta S^{\ddagger} = 4.8$ (2.8) e.u. , $\Delta G^{\ddagger}_{338} = 22.4$ (1.3) $\text{kcal}\cdot\text{mol}^{-1}$ for norbornene polymerizations performed with **9a** compared to values of $\Delta H^{\ddagger} = 27.1$ (0.5) kcal mol^{-1} , $\Delta S^{\ddagger} = 9$ (4) e.u. , and $\Delta G^{\ddagger}_{338} = 24$ (1) kcal mol^{-1} reported for ROMP catalyzed by titanacyclobutanes.



11a, 12a: Ar = 2,6- $i\text{Pr}_2\text{C}_6\text{H}_3$

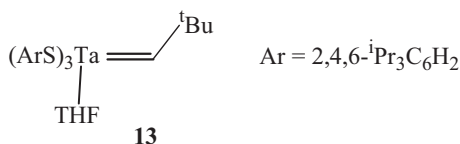
11b, 12b: Ar = 2,6-Me $_2\text{C}_6\text{H}_3$

However, this polymerization system does not meet all the requirements for a living polymerization, even though the product molecular weights increase linearly with the number of norbornene equivalents per Ta reacted. Polynorbornene samples prepared from **12a** and 200 equivalents of norbornene display narrow molecular weight distributions, with a polydispersity index M_w/M_n of 1.04, when the polymerization is stopped after 75% monomer conversion. Polymer chain growth can be terminated by the addition of aldehydes or ketones. These reagents react with the tantalacycle to produce olefin end groups via Wittig-type chemistry [59].

It is to be noted that the polydispersity index M_w/M_n increases to 1.66 when the polymerization is allowed to go to completion. M_w/M_n increases even further to

1.95 upon additional heating to 50 °C after all monomer has been consumed. This broadening of the molecular weight distribution is attributed to slow secondary metathesis. The *trans* double-bond content increases from 55% to 65% when the polymer is stored in solution for extended periods of time, which is a further indication of secondary reactions. These secondary reactions demonstrate that metathesis polymerizations with catalyst **12a** do not proceed in a living fashion.

Tantalum compounds **11a** and **12b** also catalyze ROMP of norbornene. These are nonliving polymerization systems that are more difficult to control. The molecular weight distributions of the products are generally quite broad, with polydispersity values of 4.5 and 2.7, respectively.



Tantalum alkylidene **13** contains three 2,4,6-triisopropylbenzenethiolate ligands bound to Ta and was found to be a significantly more selective metathesis catalyst than the aryloxy-based tantalum complexes **11a,b** and **12a,b** [59c]. This is attributed in part to the greater electron-donating characteristics of the thiolate ligands. Complex **13** displays very little metathesis activity toward acyclic olefins, and it does not react with ordinary alkenes such as *cis*-3-hexenes or 2-pentenenes. This tantalum-alkylidene complex polymerizes strained norbornene in a highly controlled manner, and living polymers with very low polydispersity values can be obtained. The molecular weight distributions remain narrow, with M_w/M_n values between 1.05 and 1.10, after all of the monomer has reacted. Prolonged reaction times do not affect the polydispersity or the *cis/trans* ratio of the polymer double bonds. These norbornene polymerizations differ further from those catalyzed by **12a,b** in that the tantalum-alkylidene unit represents the resting state of the catalytic cycle, and ^1H NMR resonances characteristic of a tantalacyclobutane complex cannot be detected during polymerization. The rate-determining step in polymerizations with catalyst **13** is the reaction of metal alkylidene with monomer, which causes the overall rate of reaction to be dependent on the norbornene concentration.

As observed for titanacyclobutane complexes, tantalum compounds in which tantalum is in a high oxidation state are highly reactive toward most heteroatom-containing functional groups, which limits the range of cyclic olefin monomers that can be polymerized in a living fashion by catalyst **13**.

3.2.4.3

Tungsten Catalysts

Conventional tungsten catalysts have been traditionally popular and widely used in olefin metathesis chemistry. Several commercial processes employ tungsten-based

two- and multi-component catalyst compositions [23]. However, these catalysts are generally highly Lewis acidic and display little tolerance toward functional groups. Their ill-defined composition and high activity toward metathesis of acyclic olefins limits their usefulness in polymer synthesis, when products with controlled molecular weights and low polydispersities are desired.

The first well-defined tungsten-alkylidene complexes $\text{W(=CH-}^t\text{Bu)(O)(PR}_3)_2\text{Cl}_2$ and $\text{W(=CH-}^t\text{Bu)(O)(PR}_3\text{)Cl}_2$ display only short-lived metathesis activity [44]. Other early examples of single-component tungsten-alkylidene compounds include the five- and six-coordinate alkoxide and aryloxo W(VI) complexes $\text{W(=CH-}^t\text{Bu) \cdot (OCH}_2\text{-}^t\text{Bu)}_2\text{Br}_2$, **14**, [46] and $\text{W(=CH-}^t\text{Bu)(CH}_2\text{-}^t\text{Bu)Cl(OAr)(O(ChCMe}_2)_2)$, **15** [60]. Complex **15** is highly active for metathesis of acyclic olefins and promotes secondary isomerization of alkenes, which is not suitable for living ROMP. Complex **14** displays very moderate activity that can be significantly increased by the addition of a Lewis acid component such as AlBr_3 or GaBr_3 .



Osborn, Ivin et al. conducted elegant low-temperature NMR studies on the intermediates formed during polymerizations and oligomerizations of norbornene-based monomers by the two-component system **14**/GaBr₃ (Eq. (4)) [31a, 61]. These investigations have contributed to a better understanding of the kinetic and thermodynamic factors involved in polymer chain propagation. Cationic tungstacyclobutane compound **15** slowly forms in the presence of norbornene when the temperature is raised to -53°C .

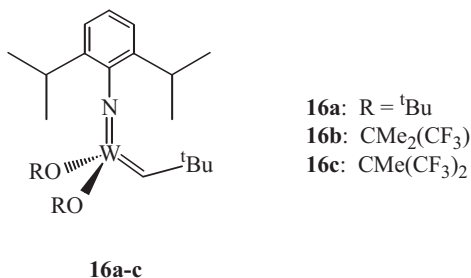
Subsequent warming to -37°C leads to ring opening of the tungstacycle, and tungsten-alkylidene and tungstacyclobutane species are formed with growing polymer chains attached. Metal-alkylidene and metallacycle species coexist below 0°C and are finally converted into the metal alkylidene upon complete consumption of the monomer.



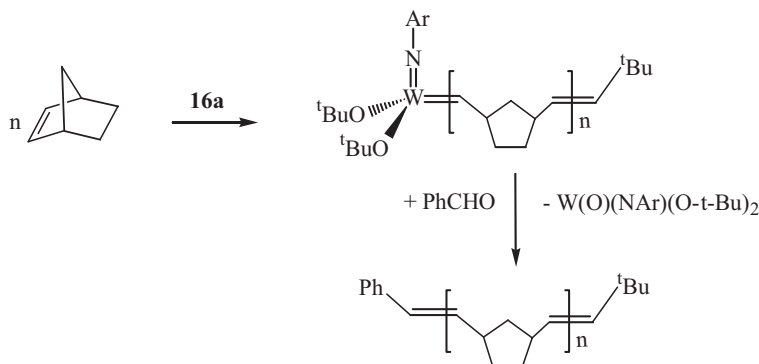
The catalyst system **14**/GaBr₃ displays some of the features of a living polymerization such as well-defined interconversion of polymerization-active intermediates and no reduction in the final NMR signal intensity for the metal alkylidene [61]. However, it is a conventional system comprised of several catalytically active components that are potentially kinetically distinct propagating species. These catalyst systems are also very active for the metathesis of acyclic olefins, and chain transfer via secondary metathesis may be difficult to detect in NMR studies. Only limited experimental data on molecular weight and molecular weight distributions are available to date [62] that could confirm that all the requirements of a living polymerization system are fulfilled.

A similar catalyst system, binaphtholato-tungsten-alkylidene complexes W(=CHPh)(Me₂BINO)(O-^tBu)₂ activated by GaBr₃, was subsequently reported by Heppert et al. [63]. Polynorbornene samples with relatively high polydispersities M_w/M_n of 1.75 and 2.03 were obtained with this catalyst, and partial polymer degradation was observed over an additional 15-min reaction period following polymer preparation.

Imido tungsten-alkylidene complexes for ROMP of norbornene Significant progress in Group 6 transition metal catalyst design for controlled ROMP was achieved by Schrock et al. [11]. They developed pseudo-tetrahedral tungsten and molybdenum complexes that are stabilized by bulky imido, alkoxide, and alkylidene ligands [11c,f, 64–66]. The metathesis activity of tungsten alkylidenes **16a–c** is strongly dependent on the electron-withdrawing character of the alkoxide ligands. Thus, the metathesis activity in the series of **16a–c** increases substantially, when changing from the *tert*-butoxide to the OCMe(CF₃)₂ ligands, as the transition metal becomes more electrophilic [65b]. The hexafluoro-*tert*-butoxide-based tungsten-alkylidene complex **16c** is a very active catalyst for the metathesis of acyclic olefins. This catalyst metathesizes *cis*-2-pentene at a rate of approximately 1000 turnovers per minute at 25 °C, which contrasts with a rate of ~100 turnovers per minutes for the trifluoro-*tert*-butoxide-based catalyst **16b**. No significant amount of reaction can be detected over a period of 1 day (at 25 °C) when the *tert*-butoxide complex **16a** is used [65b].



However, **16a**, reacts with the strained double bonds of norbornene, and living polymerization is achieved at 25 °C [67]. The polymerization mixture gives rise to a characteristic ¹H NMR doublet at δ 8.36 ppm that corresponds to the active tung-

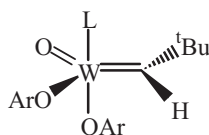


Scheme 3.2-11. Living polymerization of norbornene with tungsten-alkylidene complex **16a**.

sten-alkylidene end group of the polymer chain. Similar to the previously described Ti- and Ta-catalyzed reactions, the living polymers readily react with benzaldehyde. This Wittig-type reaction can be employed for end capping the polymerization-active chain ends (Scheme 3.2-11). The polydispersities are as low as 1.03 when the average degree of polymerization is adjusted to 500.

The more active complexes **16c** and **16b** are much less selective and react with the C=C double bonds in the growing polynorbornene chains. In addition, a significant amount of catalyst decomposition is observed in ROMP reactions that are carried out with **16c**. This catalyst produces high-molecular-weight polynorbornene at temperatures between $-20\text{ }^{\circ}\text{C}$ and $-40\text{ }^{\circ}\text{C}$ independent of the amount of monomer reacted: $M_n = 400,000$ and $M_w/M_n = 1.7$ [67]. The uncontrolled polymerization behavior is attributed to slow initiation (relative to the rate of propagation) in addition to chain transfer and termination.

Oxo-alkylidene complexes of tungsten for living ROMP Tungsten-based oxo-alkylidene complexes **17a,b** display a moderate functional group tolerance and catalyze living ROMP of 2,3-dicarbomethoxynorbornadiene, **18**, and 2,3-bis(trifluoromethyl)norbornadiene [68]. The polymerization of 100 equivalents of **18** is complete in less than 15 min, and no change in the molar mass distribution is observed when the product is isolated 45 min later. Good solubility of **poly-18** in common organic solvents allows molar mass analysis by GPC. The molar mass increases in a linear fashion with the initial ratio of monomer to initiator, and the polydispersity remains very low, with $1.01 < M_w/M_n < 1.10$ for M_n ranging from 7900 to 63,300.

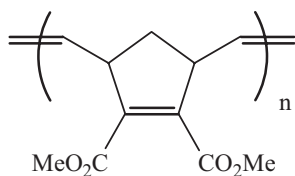


17a,b

17a: L = PMe_3

17b: L = PPh_2Me

(Ar = 2,6- $\text{Ph}_2\text{C}_6\text{H}_3$)

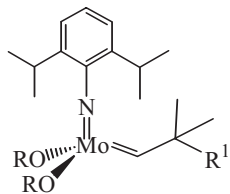


poly-18

3.2.4.4

Imido Molybdenum-Alkylidene Complexes**Polymerizations of norbornene- and norbornadiene-based monomers with Mo catalysts**

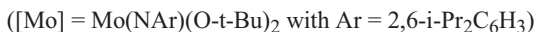
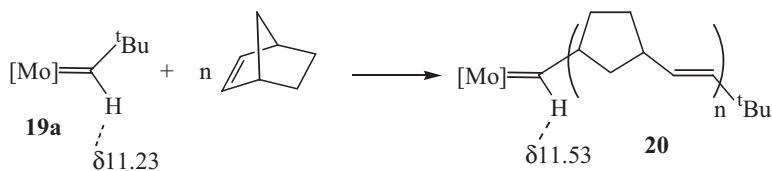
Tungsten alkylidene **16a** was a very useful catalyst in the early studies, demonstrating that structurally well-defined transition metal-alkylidene complexes are capable of initiating living ROMP. The Mo-based analogues **19a–f** show similar activities and have subsequently found much wider use than **16a** [11c,f, 66]. Even though these Mo complexes react with water and oxygen, they display a significantly improved tolerance of functional groups. Metathesis polymerizations of strained cyclic olefin monomers bearing ester, imide, and ketal substituents and of metal-containing monomers can be successfully carried out in a living manner with Schrock catalysts **19a–f**.

**19a–f****19a:** R = *t*Bu, R¹ = Me**19b:** R = C(Me)₂CF₃, R¹ = Me**19c:** R = CMe(CF₃)₂, R¹ = Me**19d:** R = *t*Bu, R¹ = Ph**19e:** R = C(Me)₂CF₃, R¹ = Ph**19f:** R = CMe(CF₃)₂, R¹ = Ph

Furthermore, Mo complexes **19a–f** appear to be less sensitive to impurities and are generally more easily synthesized, and the interconversion between molybdacyclobutane intermediates and alkylidene often occurs more readily than with the W-based counterparts.

Upon reaction of norbornene with **19a**, the ¹H NMR signal of the initiating alkylidene (δ 11.23) becomes weaker and gradually disappears. Simultaneously, a new doublet at δ 11.53 ppm appears that corresponds to the alkylidene proton of the chain-propagating end group **20** (Scheme 3.2-12) [69]. At 22 °C, 50 equivalents of norbornene are converted into polymer within 10 min (when using 0.3–4.0 M solutions of norbornene in toluene).

By reacting a given amount of monomer, generally a few equivalents, and measuring how much initiator remains unreacted, the ratio of the rate constants for propagation and initiation, k_p/k_i (or the inverse ratio, k_i/k_p), can be determined



Scheme 3.2-12. Living ROMP of norbornene with molybdenum alkylidene **19a**.



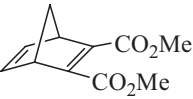
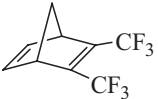
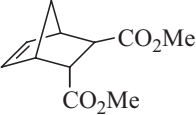
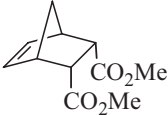
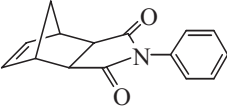
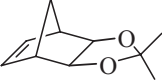
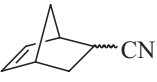
[70]. In this method, it is assumed that k_p is the same for all propagation steps independent of the chain length of the growing polymer chain.

A k_p/k_i ratio of 12.1 (corresponding to $k_i/k_p = 0.083$) was determined for the polymerization of norbornene catalyzed by **19a** in toluene at 22 °C [71]. Slower initiation reflects the greater steric bulk of the *tert*-butyl group in **19a** compared to the cyclopentylene ring linked to the alkylidene carbon of **20**. Even though the rate of initiation is approximately an order of magnitude lower than the rate of propagation, polymers with narrow molar mass distributions can be obtained, provided that a sufficiently large number of monomer molecules per initiator are reacted. Thus, polynorbornene prepared from a 50:1 mole ratio of monomer to initiator **19a** has a low polydispersity index, $M_w/M_n = 1.07$. The M_w/M_n values decrease to 1.06 and 1.04 for products obtained from 100 and 200 equivalents of norbornene, respectively. These polydispersities are similarly low as those polymers prepared from 2,3-bis(trifluoromethyl)norbornadiene, **21**, even though initiation is faster than propagation in polymerizations of **21**, with $k_p/k_i = 0.72$, which corresponds to $k_i/k_p = 1.39$ (Table 3.2-1) [69, 71b].

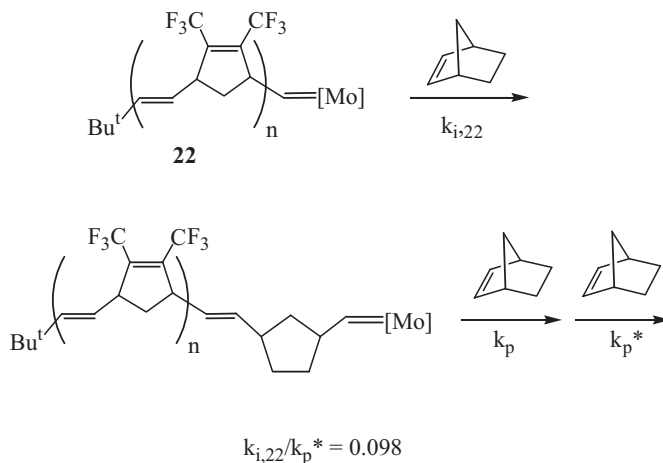
The electron-withdrawing trifluoromethyl groups have a deactivating effect on both the monomer reactivity and the activity of the chain-growing molybdenum-carbon double bonds. The combined effect of reduced monomer reactivity and alkylidene activity is reflected in a significantly reduced rate constant for propagation. The polymerization of **21** proceeds with $k_p = 0.057 \text{ M}^{-1}\text{s}^{-1}$ compared to $k_p > 2 \text{ M}^{-1}\text{s}^{-1}$ for the polymerization of norbornene at 22 °C. The difference in alkylidene activity can be estimated from the ratio of the rate constants for initiation to the rate constant for propagation, $k_{i,22}/k_p^*$, when using the living alkylidene end groups of **22** as an initiator in the polymerization of a few equivalents of norbornene (Scheme 3.2-13). At 22 °C, a $k_{i,22}/k_p^*$ ratio of 0.098 was found [71b].

Due to the low propagation rate constant k_p , polymerizations of **21** with **19a** require significantly longer reaction times for complete monomer conversions than do norbornene polymerizations. A polymer prepared from a 723:1 monomer:catalyst ratio and isolated after 24 h at 22 °C has a very narrow molar mass distribution, with $M_w/M_n = 1.04$. The molar mass of ring-opened poly(2,3-bis(trifluoromethyl)norbornadiene increases in a linear fashion with the number of monomer equivalents reacted: $M_n = 32,900$ for $[\mathbf{21}]/[\mathbf{19a}] = 153/1$, $M_n = 56,400$ for $[\mathbf{21}]/[\mathbf{19a}] = 257/1$, and $M_n = 152,200$ for $[\mathbf{21}]/[\mathbf{19a}] = 723/1$ [71b]. This indicates that living ROMP with **19a** proceeds in a very well-controlled

Tab. 3.2-1. ROMP of bicyclic olefin monomers catalyzed by **19a**.

Monomer	[M]/[19a]	M_w/M_n	k_i/k_p	trans C=C Content
	50/1	1.07	0.083	60%
	100/1	1.06		
	200/1	1.04		
	100/1	1.04	0.14	76%
	500/1	1.09		
	100/1	1.04	0.33	90–95%
	200/1	1.07		
 21	51/1	1.07	1.39	>98%
	102/1	1.05		
	202/1	1.05		
	723/1	1.04		
	50/1	1.05		
	100/1	1.04		
	200/1	1.04		
	50/1	1.11		80%
	100/1	1.12		
	200/1	1.22		
	100/1	1.07		
	100/1	1.07		60%
 (60% endo)	50/1	1.06	0.14	60%
	100/1	1.07		
	200/1	1.07		

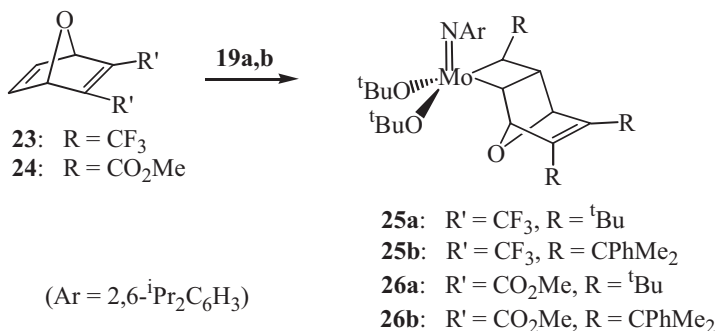
manner and is not affected by secondary reactions. By comparison, tungsten alkylidene **16a** does not polymerize **21** to give homopolymers with low polydispersities. A moderately stable tungstacyclobutane complex is formed from the reaction with 1 equivalent of **21**, which upon ring opening forms a thermally unstable tungsten-alkylidene complex [71b].



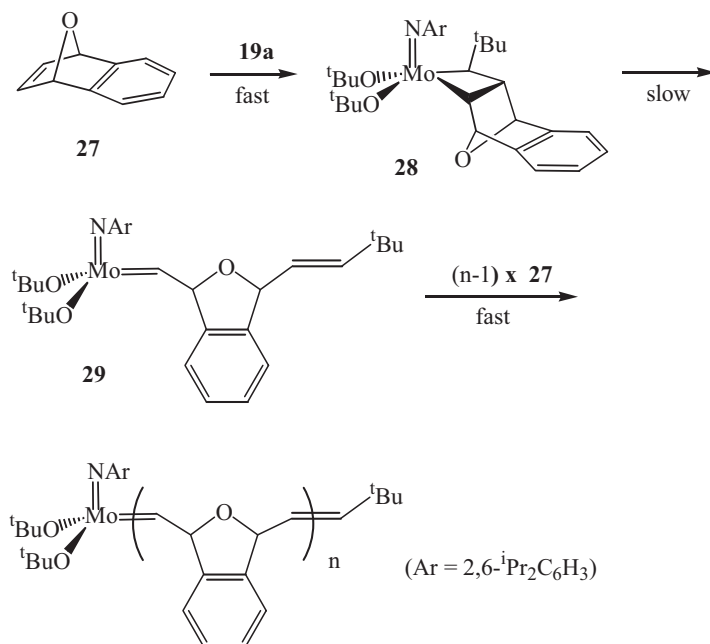
Scheme 3.2-13. Difference in the activity of molybdenum alkylidenes derived from monomer **21** and norbornene.

Other functionalized norbornene and norbornadiene derivatives that undergo living ROMP catalyzed by molybdenum alkylidene **19a** include norbornadiene-2,3-dicarboxylic acid dimethyl ester, benzonorbornadiene, 5-norbornene-*trans*-2,3-dicarboxylic acid dimethyl ester, the *exo-cis*- and *endo-cis* isomers of 5-norbornene-2,3-dicarboxylic acid dimethyl ester, 5-norbornene-*exo-cis*-2,3-diol diacetate and 5-norbornene-*exo-syn*-2,7-diol diacetate, *exo-cis*-O,O'-isopropylidene-5-norbornene-2,3-diol, 5-norbornene-2-carbonitrile, and *exo-cis*-N-phenyl-5-norbornene-2,3-dicarboximide (Table 3.2-1) [69, 71b]. All of these reactions lead to products with low polydispersities M_w/M_n between 1.04 and 1.22. Comparison of the polymers prepared from the *trans* and *endo-cis* isomers of 5-norbornene-2,3-dicarboxylic acid dimethyl ester indicate that monomers with two *endo* functionalities behave slightly less ideally than those with a single *endo* functionality. The polymerizations of norbornenediol acetates proceed in a controlled manner when THF is used as the solvent. In aromatic solvents, broadening of the molar mass distributions is observed. In general, the solvent in polymerizations of these functionalized monomers needs to be carefully selected. For example, 5-norbornene-2-carbonitrile (60/40 *endo-exo*) undergoes living polymerization in THF. However, polymerization is inhibited when toluene is used as the solvent [69].

Mo alkylidenes for living ROMP of 7-oxanorbornene and 7-oxanorbornadiene derivatives Molybdenum alkylidenes **19a,b** react with 2,3-bis(trifluoromethyl)-7-oxanorbornadiene, **23**, and 2,3-dicarbomethoxy-7-oxanorbornadiene, **18**, to form square pyramidal molybdacyclobutanes **25a,b** and **26a,b** [72]. These metallacycles are relatively stable, and polymerization does not occur (at 25 °C) in the presence of an excess of 7-oxanorbornadienes **23** and **24**.



7-Oxabenzonorbornadiene, **27**, forms a significantly less stable metallacycle, **28**, and undergoes polymerization when added to alkylidene **19a** [72]. Approximately 60% of **28** ring opens to the corresponding alkylidene within 1 h at 0 °C, compared to 75% of **25a** remaining unreacted after 24 h at 22 °C (C₆D₆). Even though complex **28** is only moderately stable, initiation of ROMP is retarded, and the polydispersity index of ring-opened poly(7-oxabenzonorbornadiene) is between 1.34 and 1.51 when 100 equivalents of **27** are polymerized in THF at 22 °C [72]. Polymerizations in benzene proceed in a less controlled manner and yield products with broader molar mass distributions, $M_w/M_n = 1.80$. Chain propagation is rapid, once metallacycle **28** is opened to alkylidene **29** (Scheme 3.2-14), and well-



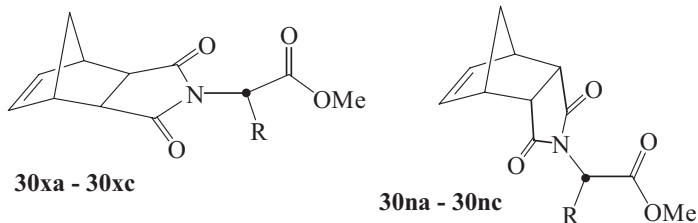
Scheme 3.2-14. Polymerization behavior of 7-oxabenzonorbornadiene.

controlled living ROMP of **27** was achieved by changing the experimental procedure. Instead of complete addition of 100 equivalents of monomer to the catalyst, only between 2 and 3 equivalents of 7-oxanorbornadiene were added initially, followed by the addition of the remaining 98 equivalents of monomer after a 20-min interval at 22 °C. The resulting product displayed a narrow molar mass distribution, with $M_w/M_n = 1.06$ [72].

2,3-*Endo-cis*-diacetox-7-oxanorbornene and *endo*-2,3-*cis*-(isopropylidenedioxy)-7-oxanorbornene polymerize readily with *tert*-butoxy-based Mo alkylidene **19a** and yield polymers with low polydispersities: $M_w/M_n = 1.17$ from 100 equivalents of the diacetox monomer and $M_w/M_n = 1.09$ from 150 equivalents of the isopropylidenedioxy derivative.

The more active trifluoro-*tert*-butoxide-based alkylidene **19d** provides efficient initiation of polymerization for the less reactive monomers **23** and **24**, and in each case, 100 equivalents of monomer are polymerized within 60 min at 22 °C. Living polymerizations are observed, and the products formed have M_w/M_n values of 1.04 and 1.15, respectively [72].

Mo-catalyzed ROMP of 5-norbornene-2,3-dicarboximide monomers The highly active hexafluoro-*tert*-butoxide-based, α -neophilidene-substituted molybdenum alkylidene **19f** can catalyze well-controlled polymerizations of monomers that display a low reactivity, provided that reaction times are kept short. Gibson and North et al. demonstrated this in recent studies on living ROMP that are aimed at devising artificial analogues of biopolymers [73]. They carried out polymerizations of *exo*- and *endo*-5-norbornene-2,3-dicarboximide compounds **30xa–30xc** and **30na–30nc**, which are derived from methyl esters of natural α -amino acids. These monomers undergo well-defined metathesis polymerizations catalyzed by molybdenum alkylidenes **19b,d,f**, and epimerization at α -stereogenic centers is not observed. In the case of the isomers of **30x,b**, products with M_w/M_n values between 1.06 and 1.15 can be obtained from polymerizations with the highly active catalyst **19f** [73b]. These low polydispersities are achieved by isolating the polymers after 30-min reaction times at room temperature. However, significant broadening of the molar mass distributions occurs over a period of 20 h due to secondary metathesis.



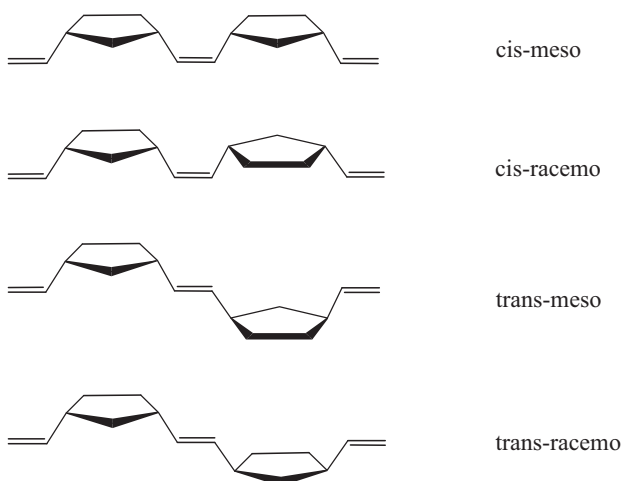
30xa, 30na: R = H
30xb, 30nb: R = CH₃
30xc, 30nc: R = CHMeEt

In parallel studies, Khosravi et al. [74] confirmed that ROMP polymerizations of *exo-n*-alkyl norbornene dicarboximides with catalyst **19a** resulted in narrow molar mass distributions ($\text{PDI} = 1.05\text{--}1.10$), while the highly active catalyst **19f** gave broader distributions ($\text{PDI} = 1.3\text{--}2.1$) after reaction times between 3 and 4.5 h.

Stereoregular polymers via molybdenum-alkylidene-catalyzed living ROMP A series of conventional catalysts was employed in the pioneering studies on the stereochemistry of ROMP polynorbornenes. Nonliving systems, e.g., ReCl_5 -based catalysts, were found that produced very regular macromolecular structures [31a]. It was subsequently discovered that structurally well-defined molybdenum alkylidenes could combine the characteristics of living ROMP polymerizations with excellent control over the polymer stereochemistry [71b, 75].

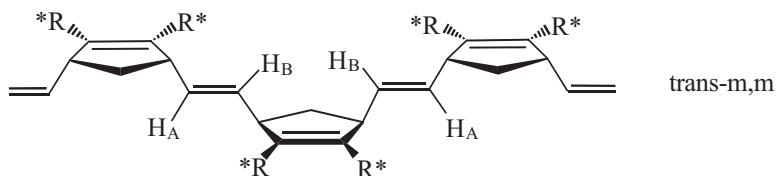
Polynorbornenes and polynorbornadienes prepared via ROMP contain olefin units flanked by chiral tertiary carbon atoms. In the case of polymers prepared from norbornene and symmetrically substituted norbornene and norbornadiene derivatives, a sequence of two neighboring repeating units can theoretically adopt any of four different isomeric structures. These are the *cis*-meso, *cis*-racemo, *trans*-meso, and *trans*-racemo diads displayed in Scheme 3.2-15 [31a]. Macromolecular products predominantly composed of meso units are called isotactic, and polymers that contain mostly racemo diads are called syndiotactic. The stereochemistry of asymmetrically substituted norbornene derivatives is more complicated, as head-head, head-tail, and tail-tail regioisomers are possible [31a].

Schrock, Feast, and Gibson et al. found that achiral Mo alkylidenes **19a** and **19b** convert bistrifluoromethylnorbornadiene, **21**, and norbornadiene-2,3-dicarboxylic esters into highly stereoregular metathesis polymers with very low polydispersity indices. These products are highly tactic and contain more than 98% *trans* vinylene

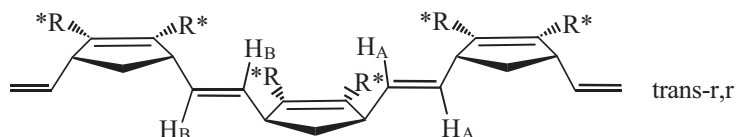


Scheme 3.2-15. Diad structures for polynorbornene prepared by ROMP.

isotactic sequence:

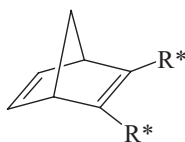


syndiotactic sequence:

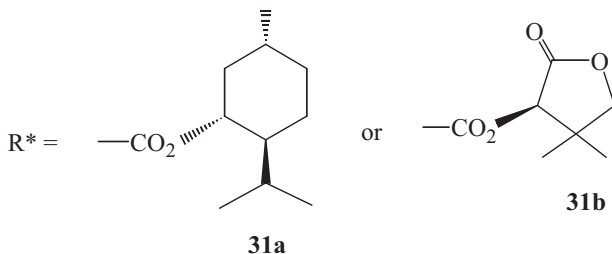


Scheme 3.2-16. Protons H_A and H_B of trans vinylene structures in polymers prepared from 2,3-disubstituted norbornadienes **31a,b** that bear chiral substituents R^* .

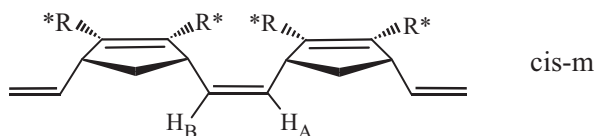
units [71b, 75]. The *trans* configuration is confirmed by the downfield ^{13}C NMR resonance of the allylic tertiary carbon atoms. The syndiotactic stereochemistry, i.e., *r*-content greater than 90%, was elucidated from measurements of the relaxed dielectric constant and from ^1H NMR analysis of ROMP polymers (Scheme 3.2-16) that were prepared from enantiomerically pure norbornadiene-2,3-dicarboxylic esters **31a** and **31b** [76].



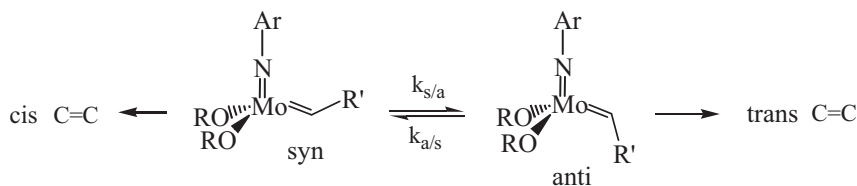
31a,b



Each vinylene unit of a *trans*-isotactic sequence in Scheme 3.2-16 bears two protons H_A and H_B that are not equivalent due to the chiral group in the substituent



Scheme 3.2-17. Cis-meso unit in polymers derived from chiral monomers **31a** and **31b**.



Scheme 3.2-18. Syn and anti rotamers of Mo alkylidenes.

R^* . In this circumstance, one might expect to see two olefin proton resonances, and the two olefin protons would be coupled. However, ^1H , ^1H COSY spectra of the highly stereoregular *trans* polymers reveal that the corresponding two olefin protons are not coupled. This demonstrates that these ROMP polymers prepared from **31a** and **31b**, and employing catalyst **19b**, are syndiotactic polymers. The *trans*-syndiotactic sequence displayed in Scheme 3.2-16 shows that the two protons H_A attached to the same vinylene unit are equivalent. The second ^1H NMR resonance is assigned to the protons H_B of the neighboring olefin unit, which are not expected to produce any detectable amount of coupling with H_A [76].

The stereochemistry of norbornadiene polymers obtained with catalysts **19e** and **19f** is confirmed in a similar manner. ROMP of monomers **18** and **21** by **19f** can be carried out in a living fashion, and high *cis* polymers (>98% *cis*) are formed that are moderately isotactic. They contain approximately 75% *m* units. COSY NMR spectra of related highly stereoregular polymers of **31a** and **31b** (>99% *cis*-meso) displayed coupling between the relevant olefin protons H_A and H_B and established the isotactic microstructure (Scheme 3.2-17) [76].

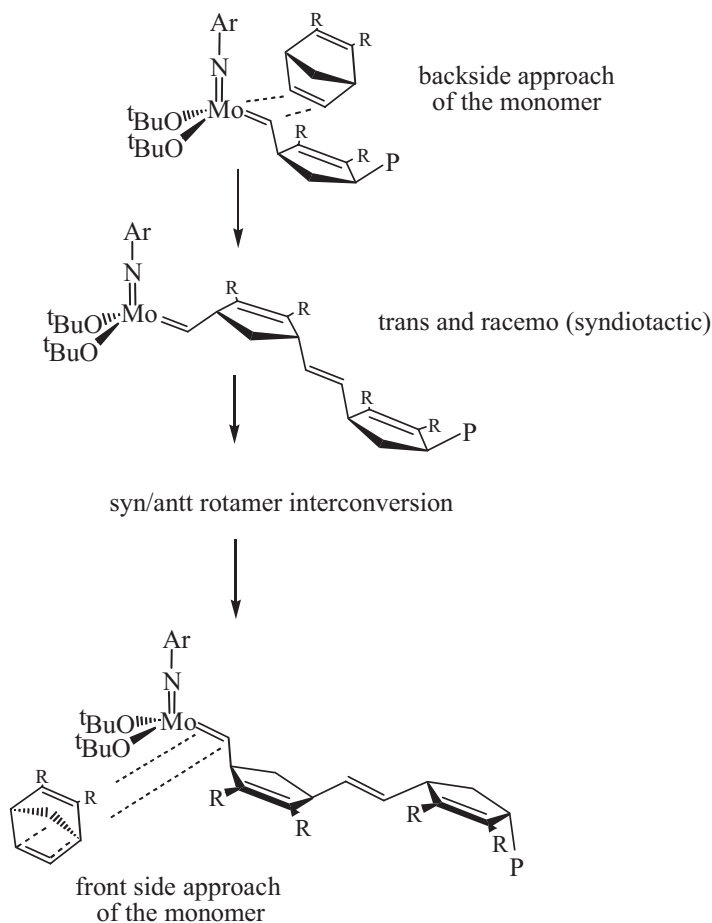
A mechanism of stereocontrol in these molybdenum-alkylidene-catalyzed polymerizations has been proposed that is based on detailed kinetic investigations [77]. Two rotameric forms of the initiating and propagating alkylidenes exist. In one of these rotamers, the alkylidene substituent R' is *syn* with respect to the imido ligand NAr , and in the other rotameric form, R' is *anti* to NAr (Scheme 3.2-18).

The *syn/anti* ratio can vary over a wide range. The *anti* isomer can be directly detected in several polymerization systems, e.g., in polymerizations of 2,3-dicarbomethoxynorbornadiene, **18**, with catalyst **19a**, but in polymerizations of monomer **21**, the concentration of the *anti* isomer is very small. It can be significantly increased after low-temperature photochemical excitation. Subsequently, the *anti* isomer is easily detected by ^1H NMR spectroscopy and metathesis reactions can be monitored [77].

The rate of rotamer interconversion was found to vary by up to 6 orders of magnitude. It is very rapid for the *tert*-butoxy-based catalysts, with $k_{s/a} \sim 1 \text{ s}^{-1}$ at 25°C ,

and relatively slow for $\text{OR} = \text{OCMe}(\text{CF}_3)_2$, with $k_{s/a} \sim 10^{-5} \text{ s}^{-1}$ at 25°C . For several catalysts, the metathesis activity of the *anti* rotamer was found to be significantly greater than the activity of the *syn* rotamer. The mechanism proposed for stereocontrol is based on the combined effects of rate of *syn/anti* isomerization and rate of chain propagation [77].

It has been suggested that the monomer approaches the chain-propagating alkylidene with its methylene bridge directed toward the arylimido ligand. In this circumstance, the *anti* rotamer produces a *trans* vinylene group, and the *syn* rotamer affords a *cis*-vinylene group. The *anti* rotamer is significantly more active, and it is proposed that propagation with Mo alkylidenes bearing *tert*-butoxide ligands occurs predominantly via reaction with the *anti* rotamer (Scheme 3.2-19), even though its concentration is very small. This reaction extends the growing



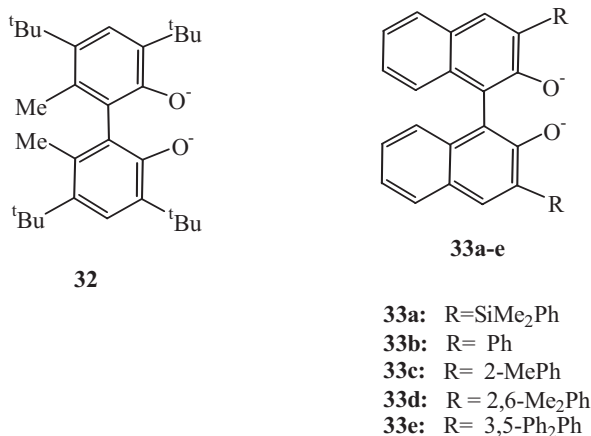
Scheme 3.2-19. Proposed chain end control mechanism in ROMP of 2,3-disubstituted norbornadienes ($\text{Ar} = 2,6\text{-i-Pr}_2\text{C}_6\text{H}_3$, $\text{P} = \text{polymer chain}$; $\text{R} = \text{CF}_3$ or CO_2Me).

polymer chain by one repeating unit and yields a *syn* alkylidene. Interconversion of the rotamers is rapid relative to chain propagation, and the next monomer molecule is very likely to react again with the *anti* form of the chain-propagating alkylidene.

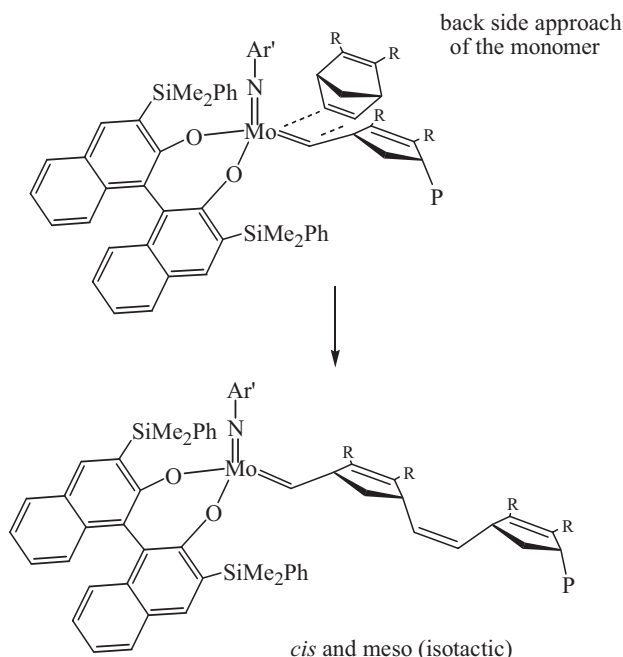
The pseudo-tetrahedral catalyst is characterized by two different CNO faces (whereby C, N, and O represent the alkylidene carbon, the imido nitrogen, and one of the two alkoxy oxygen atoms, respectively). If the monomer approaches the same CNO face in each propagation step, i.e., either always from the backside or always from the front side, an isotactic polymer is formed. If successive monomer additions occur from opposite CNO faces, as shown in Scheme 3.2-19, a syndiotactic polymer is produced. The high *trans* polymers prepared with catalysts **19a** and **19b** are found to be syndiotactic, which means that the monomer approaches the two CNO faces of the catalyst in an alternating fashion. In this way, it is the same diastereotopic face of the metal carbon double bond that is approached by the monomer, and the configuration of the polymer chain end, i.e., the configuration of the previously reacted, ring-opened monomer molecule, is controlling the polymer stereochemistry [76].

Polymerizations of 2,3-bis(trifluoromethyl)norbornadiene and 2,3-norbornadiene diesters with the hexafluoro-*tert*-butoxide-based molybdenum alkylidenes are believed to involve predominantly the *syn* rotamer, since *syn/anti* interconversions are very slow relative to chain propagation. High *cis* polymers are formed that are enriched in isotactic sequences, which indicates moderate stereocontrol via a chain-end control mechanism for achiral catalysts **19e** and **19f** [76].

The degree of isotacticity can be significantly increased by replacing the alkoxide ligands with racemic C₂-symmetric diolate ligands **32**, **33a–e**. Polymers containing more than 99% *cis* units and more than 99% isotactic structures can be obtained with Mo alkylidenes bearing the bis(silyl)-1,1'-binaphthyl-2,2'-diolate ligand **33a** (Scheme 3.2-20). It has been proposed that the asymmetric configuration of



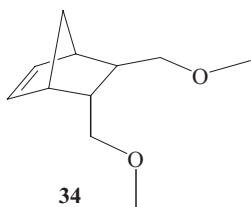
Scheme 3.2-20. C₂-Symmetric 1,1'-biphenolate and 1,1'-binaphtholates used as ligands in asymmetric Mo alkylidenes.



Scheme 3.2-21. Catalytic site control in ROMP with asymmetric catalysts ($\text{Ar}' = 2,6\text{-Me}_2\text{C}_6\text{H}_3$).

the diolate ligand is responsible for stereocontrol in this polymerization (Scheme 3.2-21), regardless of the configuration of the polymer chain end [76]. This is an enantiomorphic site-control mechanism.

Asymmetric molybdenum complexes bearing axially chiral diolate ligands based on hexaalkyl-1,1'-biphenol **32** and 1,1'-binaphthols **33a–e** also produce highly isotactic polymers from enantiomerically pure **34**. This norbornene compound bears two methoxymethyl substituents that are less electron withdrawing than the carboalkoxy and trifluoromethyl substituents of **18** and **21**. By comparison, the achiral catalysts **19e** and **19f** do not achieve this degree of stereoregularity when **34** is used as the monomer [76].



The stereoregularity of ROMP polymers also depends on the steric bulk of the arylimido ligand, the reaction temperature, and the solvent used for polymerization. Molybdenum alkylidenes bearing bulky chiral ligands and the bulky 2,6-

diisopropylphenylimido ligand produce less regular polymers than asymmetric catalysts bearing the smaller 2,6-dimethylimido ligand [78].

It is interesting to note that polymerizations of chiral monomers **31a,b** and **34** with racemic mixtures of the asymmetric Mo alkylidenes bearing ligand **33a** result in the formation of living polymers that display bimodal molar mass distributions. The average molar mass for the two fractions differs by a factor of 1.5 to 2.7. This is due to different rates of chain propagation for the two enantiomeric forms of the catalysts. Polymerizations with enantiomerically pure molybdenum alkylidenes lead to the formation of products with low polydispersities that display a single peak maximum in the GPC trace [79].

Difunctional molybdenum-alkylidene catalysts Bis(molybdenum alkylidene) complexes **36** (Scheme 3.2-22), **37a–c**, and **38** have been prepared via metathesis of the mononuclear Mo complexes **19c** and **19f** with α,ω -divinyl compounds, such as diolefin **35**, octatetraene, and 1,4-divinylbenzene, respectively [80]. Compounds **37a,b** and **38** catalyze the living polymerization of 2,3-dicarbomethoxynorbornadiene, **18**, in DME to give polymers with polydispersities of 1.18, 1.12, and 1.06, respectively (100 equivalents of monomer, 90 min at 25 °C). By comparison, a product with a relatively high polydispersity (PDI = 1.35) is obtained when the more reactive monomer methyltetracyclododecene, **39**, is polymerized with the hexafluoro-*tert*-butoxy-based catalyst **36**. *In situ* modification of catalysts **36** and **37a** via replacement of the hexafluoroalkoxy ligands by *tert*-butoxy ligands has resulted in living catalysts for tetracyclic monomer **39** (Scheme 3.2-23), and products with $M_w/M_n = 1.03$ and 1.05, respectively, are obtained from metathesis polymerizations of 200 equivalents of **39**.

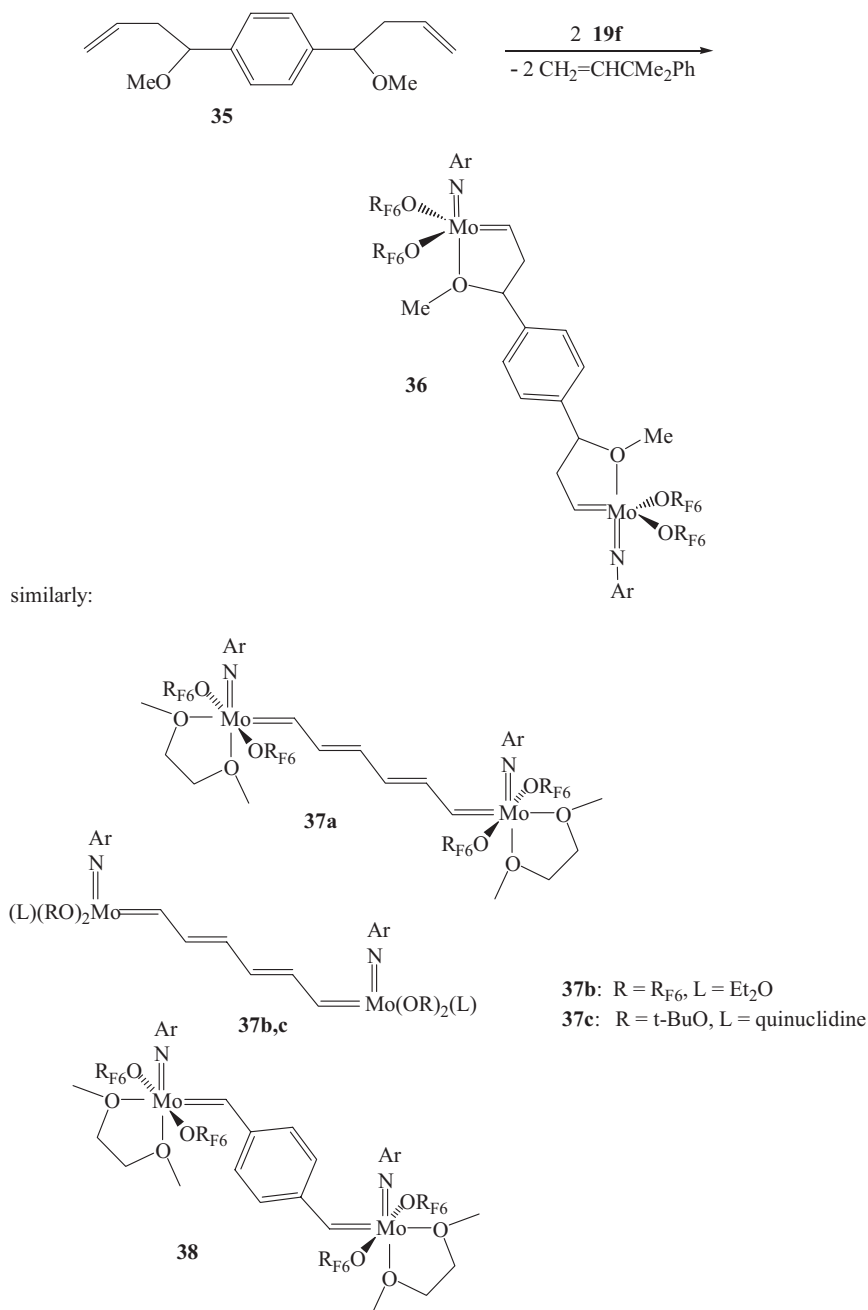
A polymer with a comparably low polydispersity (PDI = 1.07) is prepared directly from ROMP of 200 equivalents of norbornene with the *tert*-butoxy-based catalyst **37c**. End capping with benzaldehyde produces a polynorbornene that bears two phenyl end groups.

3.2.4.5

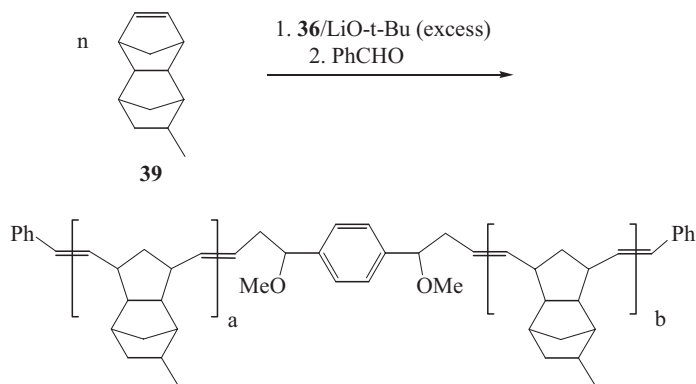
Imido Tungsten- and Molybdenum-Alkylidene Catalysts for ROMP of Monomers Containing Cyclobutene, Bicyclooctadiene, and Bicyclooctatriene Ring Systems

Cyclobutene polymerizations with tungsten alkylidene **16a** become well controlled in the presence of the donor component PMe_3 (Scheme 3.2-24). The resulting ring-opened polycyclobutene is structurally identical with strictly 1,4-enchaind polybutadiene. Polymer products with polydispersities M_w/M_n as low as 1.03 are obtained after 1 h at 25 °C when monomer:catalyst ratios between 50:1 and 200:1 and phosphine:catalyst ratios between 5:1 and 10:1 are employed [81].

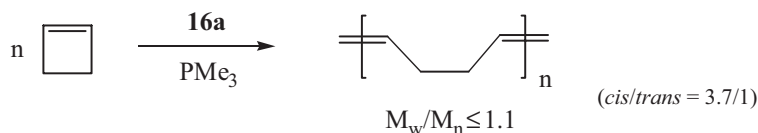
In the absence of PMe_3 , the polymerization is not controlled, and polymers with broad molar mass distributions ($M_w/M_n > 2.0$) are formed. This is a result of very slow initiation compared to chain propagation. The rate constant for propagation is approximately 10^3 greater than the rate constant for initiation at -60 °C, i.e., $k_p/k_i \sim 10^3$. Thus, the polymerization of cyclobutene by the unmodified cata-



Scheme 3.2-22. Synthesis of bis(molybdenum alkylidene) complex **36** (R_{F6} = Me(CF₃)₂C, Ar = 2,6-i-Pr₂C₆H₃).



Scheme 3.2-23. Polymerization of methyltetracyclododecene with modified catalyst **36**.

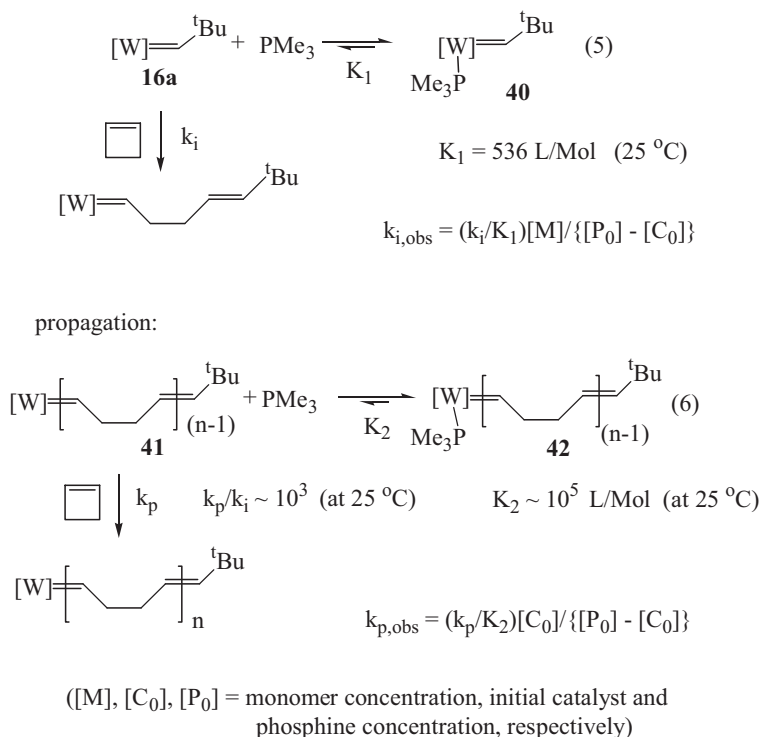


Scheme 3.2-24. Living polymerization of cyclobutene in the presence of PMe_3 .

lyst system **16a** does not fulfill all the criteria of an ideal living system. A significant amount of the catalyst remains unreacted after all of the monomer has been consumed.

Trimethylphosphine acts as a reversibly binding ligand for **16a**, and the binding constant K_1 , i.e., the equilibrium constant in Eq. (5), is 536 (mol/l)^{-1} at 25°C (Scheme 3.2-25). The bound form **40** does not polymerize cyclobutene and initiation is retarded, as only a small fraction of the active catalyst is available for initiation at any given time. It is to be noted that binding of the phosphine ligand is substantially stronger in tungsten-alkylidene species **42** than in complex **40**, and K_2 is approximately $10^5 \text{ (mol/l)}^{-1}$ in Eq. (6). This difference in binding can be explained by the greater steric bulk of the *tert*-butyl substituent compared to the linear polymer chain attached to the alkylidene carbon in **42**. The stronger binding to the chain propagating components means that the rate of propagation is reduced to a significantly greater extent than the rate of initiation (Scheme 3.2-25). Thus, the polymerization with **16a**/ PMe_3 becomes living as a result of a more effectively reduced rate of propagation. For the phosphine-modified system, $k_{i,\text{obs}}$ is greater than $k_{p,\text{obs}}$, and none of the initial alkylidene catalyst is detected after 20 equivalents of cyclobutene have reacted. No decomposition of the propagating alkylidene **42** can be observed over a 2-week period, indicating the absence of chain-termination processes [81].

Living ROMP of cyclobutene can also be achieved by the addition of phenyldimethylphosphine. However, a larger amount of this phosphine is required. A polycyclobutene sample with $M_n = 147,000$ and $M_w/M_n = 1.10$ is obtained from the polymerization of 1500 equivalents of cyclobutene at 0°C in the presence of 75



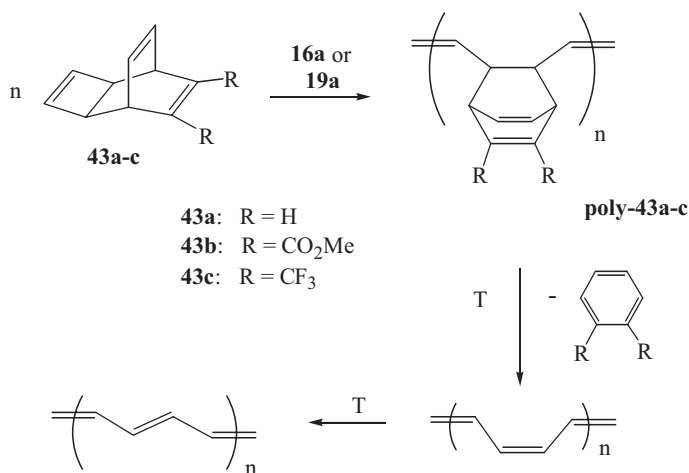
Scheme 3.2-25. Initiation and propagation in cyclobutene polymerization in the presence of PMe_3 .

equivalents of $PPhMe_2$. THF, pyridine, quinuclidine, and diphenylmethylphosphine are less effective donor components, and polymers with broader molar mass distributions, $M_w/M_n > 1.5$, are formed [81].

A reaction sequence involving living ROMP of cyclobutene followed by hydrogenation of the polymer double bonds has been used for the preparation of perfectly linear and essentially monodisperse polyethylene (Eq. (7)). Successive additions of norbornene, PMe_3 , cyclobutene, and norbornene have led to the formation of ABA-type triblock copolymers [82].



7,8-Bis(trifluoromethyl)tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene **43c** contains a strained cyclobutene ring that is condensed to a bicyclo[2.2.2]octadiene unit. Early studies by Feast et al. showed that this monomer could be polymerized with conventional metathesis catalysts [83]. Subsequently, W and Mo alkylidenes **16a** and **19a** were found to catalyze the living polymerization of **43c**. These *tert*-butoxy-based catalysts



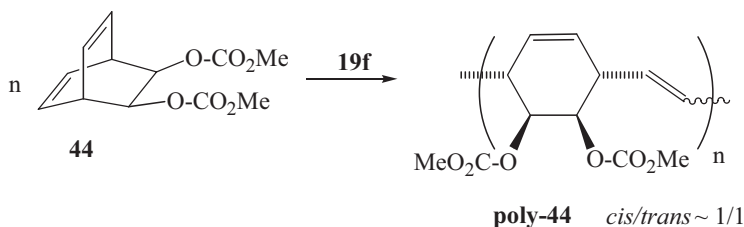
Scheme 3.2-26. ROMP of tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene monomers.

selectively react with the 4-membered ring of the monomer (Scheme 3.2-26) [84]. The other two cyclic double bonds do not undergo any detectable amount of ring opening under the reaction conditions employed (in toluene or THF, 15–35 min at 25 °C), and non-cross-linked, soluble samples of **poly-43c** are formed. These products are oligomeric or polymeric, depending on the monomer:catalyst ratios used. The Mo-based catalyst **19a** is preferred over tungsten alkylidene **16a**, as the resulting molybdenum-alkylidene end groups of the polymer are more stable and greater control over the polymerization behavior is achieved. A k_i/k_p ratio of 0.56 has been determined for the monomer/catalyst pair **43c/19a**.

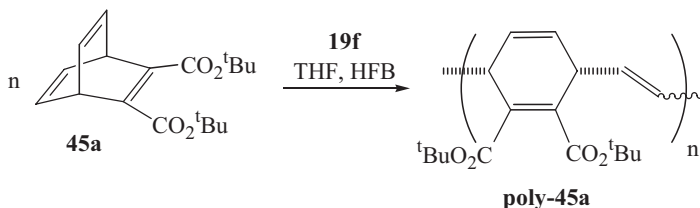
Polymer samples of **poly-43c** with the following polydispersities have been reported: $M_w/M_n = 1.16$ from an initial monomer:catalyst ratio of 30:1, and $M_w/M_n = 1.15, 1.11,$ and 1.18 from 60, 150 and 250 equivalents of **43c**, respectively [84b]. The slight broadening of the molar mass distributions is attributed to a small amount of retro-Diels-Alder reaction and subsequent secondary reactions that occur at 25 °C. The retro-Diels-Alder reaction can be carried out in a controlled manner by heating to temperatures between 85 °C and 120 °C, and infusible polyacetylene is formed (Scheme 3.2-26).

Both the methyl carboxylate **43b** and the parent hydrocarbon compound **43a** have been found to give low polymer yields in ROMP reactions with **16a** and **19a**.

The hexafluoro-*tert*-butoxy-based Mo catalyst **19f** is significantly more active than **19a** and is capable of ring opening the bicyclo[2.2.2]octadiene ring system at a temperature of 25 °C. For example, the *cis*-bis(methoxycarbonyloxy)-substituted bicyclo[2.2.2]octadiene compound **44** undergoes well-defined ROMP in the presence of catalyst **19f** (Scheme 3.2-27), and quantitative polymer yields are obtained (120 equivalents of **44** in CH₂Cl₂, 24 h at 25 °C) [85]. The resulting product, **poly-44**, displays slightly broadened molar mass distributions. Polymer samples prepared from 100 equivalents of monomer have the following molar mass character-



Scheme 3.2-27. ROMP of a bicyclo[2.2.2]octadiene monomer.



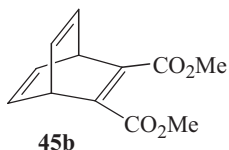
Scheme 3.2-28. ROMP of a tert-butyl-substituted bicyclo[2.2.2]octatriene monomer (HFB = hexafluoro-*tert*-butanol).

istics: $M_n(\text{GPC}) = 63,000$ with $M_w/M_n = 1.34$ when CH_2Cl_2 is used as the solvent, and $M_n(\text{GPC}) = 46,000$ with $\text{PDI} = 1.23$, when the polymerization is carried out in THF. The monomer:catalyst ratio can be increased to 250:1, without broadening of the molar mass distribution occurring. By comparison, polymerization of the related bis(acetate) of bicyclo[2.2.2]octa-5,8-diene-*cis*-2,3-diol ceases after only a few equivalents of monomer have been consumed.

Poly-44 can serve as a precursor material for a controlled synthesis of poly(1,4-phenylenevinylene) (PPV). This transformation involves thermally induced elimination of carbon dioxide and methanol.

Similar to **44**, di-*tert*-butyl bicyclo[2.2.2]octa-2,5,7-triene-2,3-dicarboxylate, **45a** (a barrelene derivative), is polymerized in a living fashion by Mo catalyst **19f**. It forms a polymer consisting of an alternating sequence of vinylene and 1,4-enchaind cyclohexadiene units, **poly-45a** (Scheme 3.2-28) [86]. A reaction time of 36 h is required for converting 45 equivalents of barrelene **45a** into polymer at 25 °C. Only 77% of the initial amount of catalyst **19f** has been found to initiate before all of the monomer has been consumed. The rate of reaction is significantly increased in the presence of 15 equivalents of hexafluoro-*tert*-butanol (HFB), and polymerization reaches completion within 3 h at 25 °C (45 equivalents of **45a**), with 86% of catalyst **19f** initiating. The molar mass data are: $M_n(\text{GPC}) = 34,700$ with $M_w/M_n = 1.15$ in the absence of HFB and $M_n(\text{GPC}) = 19,600$ with $M_w/M_n = 1.22$ for **poly-45a** prepared in the presence of 15 equivalents of HFB. By comparison, polymerization of the less bulky dimethyl bicyclo[2.2.2]octa-2,5,7-triene-2,3-dicarboxylate, **45b**, with **19f** (plus 15 equivalents of HFB) proceeds at a significantly reduced rate, and the ROMP of 45 equivalents of this monomer reaches only 80–90% completion after 1 week at 25 °C. The lower rate is attributed

to coordination of monomer and/or polymer chain segments to the propagating metal alkylidene [86].

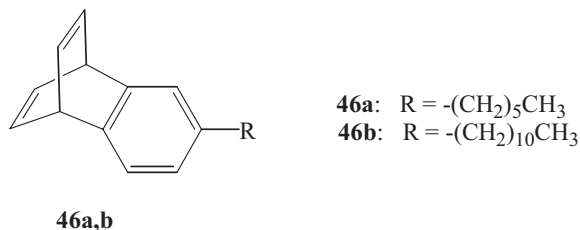


The polymerization conditions for **45a** are further optimized by adding 25 equivalents of THF to the reaction mixture of monomer, catalyst, and HFB. THF reversibly coordinates to Mo, and propagation is more effectively retarded than initiation, thereby leading to more efficient initiation. The resulting product **poly-45a** displays a lower polydispersity index: $M_n = 17,800$ with $M_w/M_n = 1.11$ from 45 equivalents of **45a** (100% initiation). Complete initiation can also be achieved in the absence of THF by reacting a larger amount of monomer, e.g., 99 equivalents of **45a** in the presence of 15 equivalents of HFB: $M_n = 39,300$ with $M_w/M_n = 1.15$.

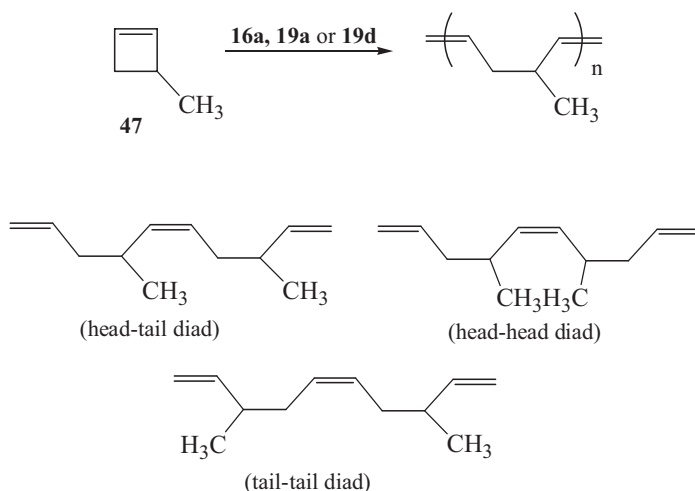
The livingness of this polymerization (Scheme 3.2-28) has been confirmed by demonstrating that chain growth resumes after a second batch of monomer has been added, and the final product displays an increased molar mass without significant broadening of the molar mass distribution. The polydispersity also remains low.

Poly-45a has been subsequently converted into a water-soluble poly(1,4-phenylene vinylene) derivative. This has been achieved by employing a reaction sequence involving polymer oxidation, acidic removal of the *tert*-butyl substituent, and basic hydrolysis of the anhydride units formed [86].

Imido molybdenum alkylidene **19f** polymerizes benzobarrelene derivatives **46a** and **46b**. However, it has been found that these Mo-catalyzed polymerizations do not proceed in a well-controlled manner, and products with very broad molar mass distributions, $M_w/M_n \sim 5$, are obtained [86].



W- and Mo-based alkylidene complexes **16a** and **19a** catalyze the ring-opening polymerization of 3-methylcycobutene, **47**. The resulting ROMP products are atactic and display an irregular structure that consists of approximately equal amounts of head-tail, head-head, and tail-tail units (Scheme 3.2-29) [87]. These polymerizations have not yet been optimized with respect to livingness. The tungsten catalyst yields a product with a slightly broadened molar mass distribution, $M_w/$



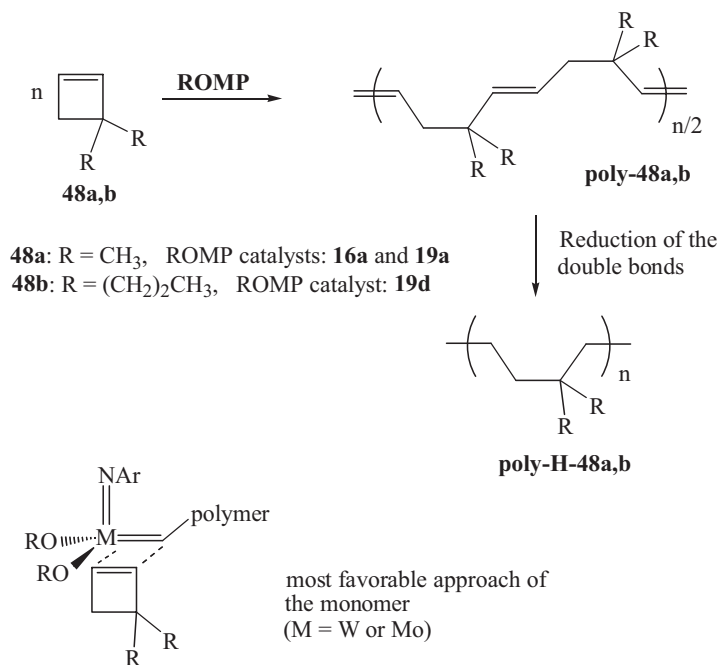
Scheme 3.2-29. ROMP of 3-methylcyclobutene with W and Mo alkylidenes **16a** and **19a** yielding a polymer with irregular regioregistry.

$M_n = 1.38$ from the polymerization of 212 equivalents of **47** (0.5–1.0 h at 25 °C), and the molybdenum catalyst **19a** forms a polymer with a broad molar mass distribution, $M_w/M_n = 2.46$ from 207 equivalents of **50**. These polymers contain 79% and 84% *cis* double bond structures, respectively. Initial results indicate that polymers with narrow molar mass distributions can be obtained when 50 equivalents of PPhMe₂ are added to Mo alkylidene **19d** prior to the addition of monomer **47**.

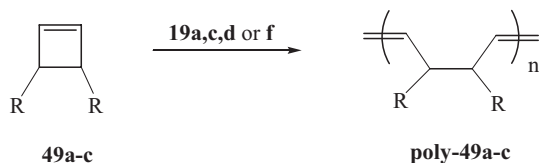
Polymerizations of 3,3-dimethylcyclobutene and 3,3-di-*n*-propylcyclobutene, **48a,b**, have been carried out with both catalysts **16a** and **19a** (Scheme 3.2-30). These reactions proceed in a highly regioselective fashion, which contrasts with ROMP of the monosubstituted cyclobutene derivative **47**. The very regular products **poly-48a** and **poly-48b** are obtained that contain almost exclusively head-tail-linked structures and *trans* olefin units [87]. Subsequent hydrogenation leads to the formation of saturated polymers that may display interesting properties due to their conformationally constrained structures [87b]. The hydrogenated product of ring-opened poly(3,3-dimethylcyclobutene), **poly-H-48a**, can be described as a strictly alternating ethylene-isobutylene copolymer.

The ROMP reactions of **48a** and **48b** have been carried out in the absence of a phosphine base. These polymerizations lead to products with M_w/M_n values between 1.3 and 1.6 (when $M_n(\text{GPC})$ is between 11,700 and 51,700), which indicates that polymerization is not as well controlled as cyclobutene polymerizations that are performed with the modified catalyst system **16a**/PMe₃.

Carboxylic ester and benzyloxy-functionalized polybutadienes have been prepared via ROMP of 3,4-disubstituted cyclobutenes **49a–c** (Scheme 3.2-31). These are well-controlled living polymerizations when molybdenum alkylidenes **19a** and **19d** are employed as the catalysts [88]. The molar mass distributions of polymers



Scheme 3.2-30. ROMP of 3,3-dialkyl substituted cyclobutenes and subsequent reduction of the ring-opened polymers.



Scheme 3.2-31. Functionalized polybutadienes via ROMP of cyclobutene derivatives.

prepared from 30–120 equivalents of monomer are quite narrow, with polydispersity indices between 1.04 and 1.15. The polydispersity index remains narrow for polymerizations performed with higher monomer:catalyst ratios, and ROMP reactions employing up to 500 equivalents of monomer have been investigated. The livingness of these Mo-catalyzed polymerizations is due to relatively low rates of chain propagation. The polymerizations of dibenzyl ether derivative **49c** and norbornadiene diester **18** have been observed to proceed with approximately similar propagation rate constants. The diethyl ester derivative **49a** polymerizes approximately 1 order of magnitude more slowly than norbornadiene derivative **18**. The rate constant is further decreased by a factor of approximately 7 in polymer-

izations of the dibenzylester **49b**. The reduced rates have been rationalized in terms of reduced monomer reactivity caused by the electron-withdrawing nature and the steric bulk of the monomer substituents [88b]. Later studies by others have demonstrated that chelation involving functional groups on the growing polymer chain also plays an important role. These results are described in the section titled “Monomers containing unsaturated 4- and 8-membered ring structures and their polymerization behavior.”

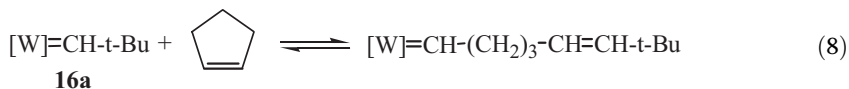
Polymerizations of **49a–c** with the more active hexafluoro-*tert*-butoxy-based catalysts **19c** and **19f** are not as well controlled as the polymerizations catalyzed by **19a,d**, and polymers with broadened molar mass distributions, M_w/M_n between 1.2 and 1.4, are obtained. On the other hand, functionalized polybutadienes **poly-49a–c** prepared with the more active catalyst are more stereoregular and contain up to 91% *cis* olefin units.

The polymerizations of cyclobutenes **49b** and **49c** with Mo-alkylidene catalysts offer indirect routes to hydroxy- and carboxylic-acid-functionalized polymers, as the benzyl groups can serve as protecting groups that are removed upon treatment with iodotrimethylsilane followed by hydrolysis with MeOH [88b].

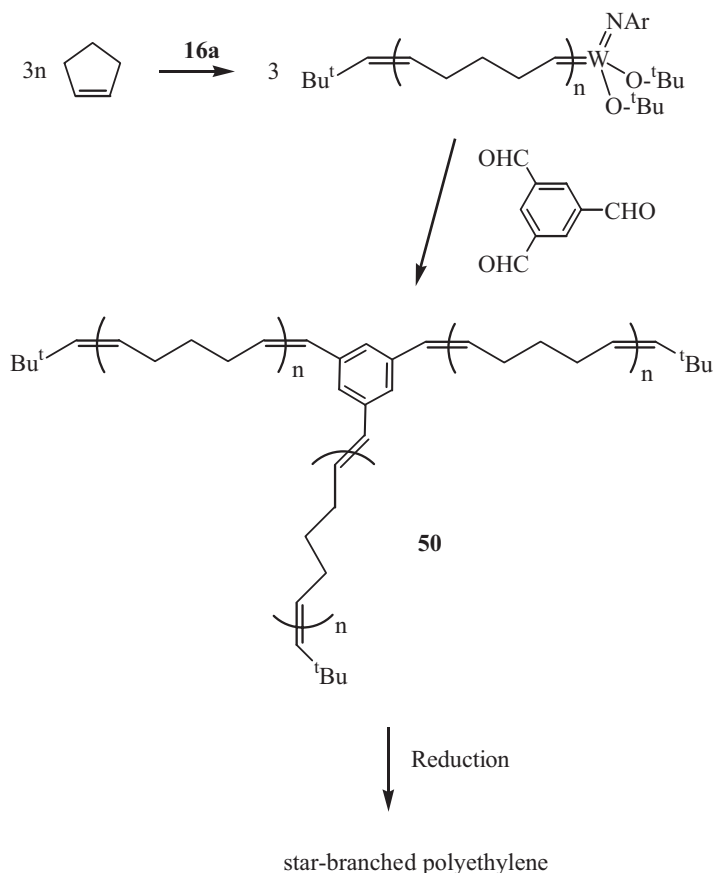
3.2.4.6

Tungsten- and Molybdenum-Alkylidene Catalysts in Cyclopentene Polymerizations

Cyclopentene is considerably less strained than cyclobutene, and chain propagation initiated by **16a** proceeds in a reversible fashion (Eq. (8)). The final equilibrium mixture of an originally 2 molar monomer solution contains only approximately 5% polymer at 60 °C, while at –60 °C the reaction mixture contains approximately 95% ring-opened polycyclopentene [89]. Polymerization is reversed upon applying vacuum to the product mixture, and the original initiator **16a** is reformed. At 25 °C, cyclopentene polymerizations are also affected by gradual decomposition of the chain-propagating alkylidenes, and products with relatively high polydispersities ($1.4 < M_w/M_n < 1.8$) are formed.



Polymer samples with narrow molar mass distributions, $1.08 \leq M_w/M_n \leq 1.20$, can be prepared by polymerizing relatively concentrated monomer solutions ($[M] > 2.0$ molar) with **16a** at a low temperature of $T \leq -40$ °C [89b, 90a]. After reaction periods of less than 24 h, these polymerizations are terminated via reaction with aldehyde compounds in order to prevent broadening of the molar mass distributions. Low-temperature coupling with 1,3,5-benzenetricarboxaldehyde leads to the formation of star-branched polymer **50**, and subsequent reduction of the double bonds affords polyethylene with a three-armed star structure (Scheme 3.2-32) [90a]. Upon coupling, the molar mass M_n increases, and the molar mass distributions are moderately broadened, yielding products with M_w/M_n between 1.5 and 1.6.



Scheme 3.2-32. Star-branched polymers via ROMP with tungsten alkylidene **16a** (Ar = 2,6-*i*-Pr₂C₆H₃).

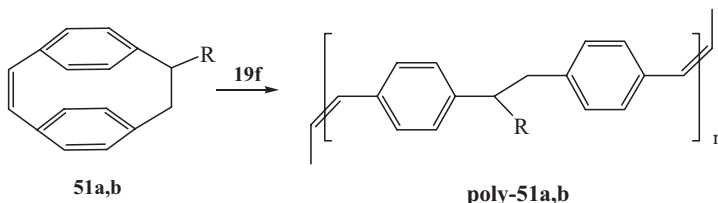
Subsequently, metathesis polymerizations of cyclopentene were carried out with Mo-neophilidene catalyst **19d** at a reaction temperature of 25 °C. Polymers with narrow molar mass distributions can be prepared through careful adjustment of the reaction conditions, even though this polymerization does not fulfill all of the criteria for a living polymerization [90b]. Products with M_n (GPC) between 14,200 and 67,800 and polydispersities between 1.04 and 1.10 have been obtained by limiting the monomer conversion to less than 20% and simultaneously utilizing the retarding influence of PMe₃. Successive reduction of the ring-opened polycyclopentene gives polyethylene with a narrow molar mass distribution.

3.2.4.7

Paracyclophene Polymerizations

Olefin metathesis polymerization of [2.2]paracyclophan-1-ene, **51a**, and 9-[(*tert*-butyldimethylsilyl)oxy][2.2]paracyclophan-1-ene, **51b**, can be performed in a living

fashion with the hexafluoro-*tert*-butoxy Mo-neophilidene catalyst **19f** [91]. These polymerizations are relatively slow, even though the ROMP catalyst employed is very active. A reaction time of 24 h at 25 °C is needed in order to convert 100 equivalents of **51a** into **poly-51a**. The reduced rate of polymerization is caused by the steric interactions between the *ortho* hydrogens of the paracyclophenes and the bulky ligands of the catalyst. The poly([2.2]paracyclophan-1-ene) prepared from 100 equivalents of **51a** displays a relatively low polydispersity index of 1.2 and a molar mass M_n of 26,000, indicating well-controlled polymerization behavior.



51a: R = H

51b: R = ^tBuMe₂SiO

Scheme 3.2.33. Living ROMP of paracyclophenes.

Polymerization with **19f** proceeds in a highly stereoselective manner, and the resulting polymers, **poly-51a,b**, contain approximately 98% *cis* olefin units. The siloxy-substituted polymer **poly-51b** contains approximately equal amounts of head-head and head-tail units.

Other Mo and W alkylidenes have been found to produce insoluble polymers of **poly-51a**, and it is assumed that precipitation of the ROMP product during polymerization is due to a larger *trans* olefin content of the products. Photolysis and reactions with a catalytic amount of iodine cause isomerization to the *trans* polymers. Treatment with HCl at 190 °C leads to simultaneous *cis/trans* isomerization and desilylation, combined with dehydration, and affords poly(*p*-phenylenevinylene) [91a].

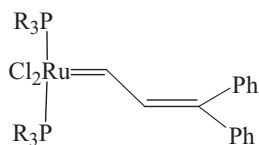
3.2.4.8

Ruthenium Catalysts and Living ROMP

The development of well-defined ruthenium catalysts and their application to the field of metathesis chemistry have become the focus of much research in recent years [11a]. These catalysts have tremendous potential for increasing the practical scope of the metathesis reaction due to their coincident functional group tolerance and high activity. Thus, these complexes – while highly active in catalyzing the olefin metathesis reaction – have also proven to be highly selective for this particular reaction, thereby extending its scope beyond simple olefins to functionalized ones. They tolerate most functional groups, including hydroxyl, aldehyde, ketal, nitro, sulfonate, carboxylic acid, and carboxylic acid derivatives. The advantages of

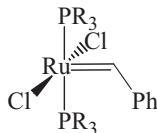
living polymerization over nonliving – control over molecular weight, narrow molecular weight distribution, and the potential for the synthesis of more advanced macromolecular architectures – are clear. When these are combined with the above-mentioned advantages of ruthenium-based metathesis catalysts, ROMP becomes an extremely versatile tool in the synthesis of functionalized polymers with well-ordered structures and well-regulated molecular weights.

Conventional ruthenium catalysts such as $[\text{Ru}(\text{H}_2\text{O})_6(\text{tos})_2]$ (tos = *p*-toluene-sulfonate) will initiate metathesis, but the active species is ill-defined, and it is difficult to control molecular weights and weight distributions [38e]. The early-generation Grubbs catalysts **52a** and **52b** were the first ruthenium complexes that were found to catalyze ROMP in a well-controlled manner [92].



52a: R=Ph

52b: R=Cy



53a: R=Ph

53b: R=Cy

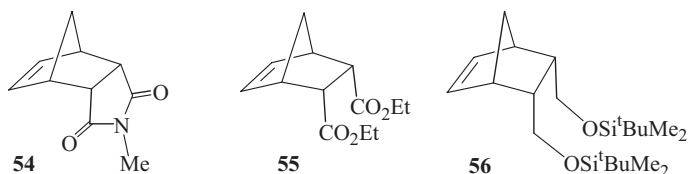
Polymerization of norbornene and norbornene derivatives Complex **52a** polymerizes norbornene in a controlled fashion, as evidenced primarily by the synthesis of a block copolymer using norbornene and 2,3-dideuteronorbornene [92a], giving a product polymer with a polydispersity (PDI) of 1.25 [93]. The reaction was monitored using ^1H NMR spectroscopy, and the signal assigned to the proton of the propagating carbene was observed to disappear upon addition of the deuterated norbornene and reappear upon addition of the non-deuterated monomer. The implication of this is that when all of the monomer is consumed, the polymer chains remain attached to the catalytic center such that propagation is merely suspended until more monomer is added, proving that termination and chain transfer are absent.

However, in the case of functionalized norbornenes **54** and **55**, the electron-withdrawing substituents on the ring decrease the amount of electron density localized in the double bond, thereby decreasing the ability of the monomer to coordinate to the ruthenium center. As a result, complex **52a** cannot polymerize either monomer, as it is not sufficiently active [94]. Replacement of the triphenylphosphine ligands with tricyclohexylphosphines produces catalyst **52b**, which displays an overall significantly increased activity due to the greater electron-donating ability of the cycloalkyl substituents [92b]. (Ruthenium vinylalkylidene complex **52b** exists in two isomeric forms: the two phosphine ligands are *trans* to each other in approximately 84% of the alkylidene, and in the minor form, ~16%, they are *cis*.)

The tricyclohexylphosphine-based catalyst **52b** catalyzes ROMP of monomers **54** and **55** [94]. The polymerization of **54** leads to a product that contains high molar mass byproducts in addition to a main fraction with a narrow molar mass

distribution. The polymerization of *endo*-norbornene diester **55** is living, and a polymer with an $M_n(\text{GPC})$ of 56,400 and M_w/M_n of 1.11 is obtained from a monomer:catalyst ratio of 150:1 after 4 h at 50 °C. But, in the ROMP of norbornene using **52b**, the rate of propagation is much higher than the rate of initiation and secondary metathesis reactions occur [92b]. As a result, ROMP of norbornene is nonliving when carried out with complex **52b**.

Both **52a** and **52b** catalyze the living ROMP of the silylated monomer **56** [94], but the difference in the activities of the two catalysts is reflected by the differing reaction conditions required to produce polymers with the same PDI of 1.2. In the case of catalyst **52a**, the reaction time is significantly longer than for **52b** (more than 5 h compared to 0.5 h for polymerizations of 115–225 equivalents of monomer), and a higher temperature is required (60 °C compared to 50 °C). At a lower temperature of 23 °C, the polymerization of **56** with **52b** affords a polymer with a higher PDI of 1.49 as a result of less-effective initiation.



The later-generation Grubbs catalysts, **53a** and **53b**, incorporate a benzylidene moiety and are more readily synthesized than **52a,b** [93]. They have proven to be more active than the first-generation catalysts, as illustrated by the fact that k_i for **53a** is approximately 1000 times that for **52a** in the ROMP of norbornene [95]. The PDI of the product polymer is also significantly lower in the case of **53a** than in that of **52a**: 1.04 versus 1.25 [93]. The activities of complexes **53a** and **53b** follow the same pattern as above. Complex **53a** catalyzes the living ROMP of norbornene and various cyclobutene derivatives, whereas **53b** is living for functionalized norbornenes and 7-oxanorbornenes but not for norbornene itself [93].

The main characteristics of norbornene polymerizations catalyzed by **52a,b** and **53a,b** are summarized in Table 3.2-2. The polymerization-active end group in ruthenium-catalyzed polymerizations is commonly removed by reaction with ethyl vinyl ether, which produces an olefin end group on the polymer chain end and an inactive Fischer carbene, $(\text{PR}_3)_2\text{RuCl}_2(=\text{CH}-\text{O}-\text{Et})$.

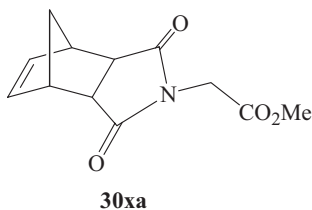
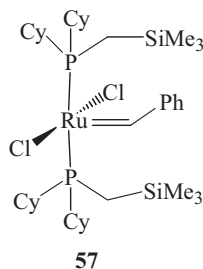
Tab. 3.2-2. Polymerizations of norbornene with Ru catalysts **52a,b** and **53a,b** (25 °C).

Catalyst	turnover freq. (equiv/h)	k_i/k_p	M_w/M_n^a
52a	23	0.006	1.25
52b	8,400		2.65
53a	150	9.0	1.04
53b	$>10^4$		2.0–2.5

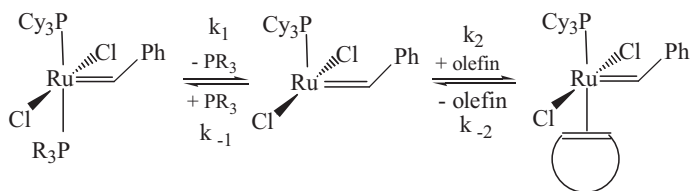
^a polymerization of ~100 equiv of monomer

If the catalyst is too active under a given set of conditions and using a given monomer, it will not be possible to exert control over the polymerization. However, the catalyst must be sufficiently active to react with the selected monomer.

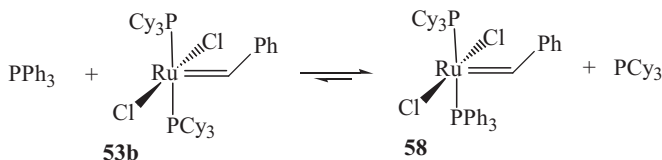
The performance of ruthenium-benzylidene complexes can be fine-tuned by modifying or changing the phosphine ligands. ROMP of norbornene-imide monomers derived from amino esters sometimes gave polymers with moderately broadened molecular weight distribution when complex **53b** was used as the initiator. The structure of the phosphine ligands was varied by replacing one of the cyclohexyl substituents on each phosphorus with a CH_2SiMe_3 group [96]. This yielded complex **57**, which provided greater control over the ROMP of imide-substituted monomers while remaining highly active. A comparative study of the polymerization of monomer **30xa** by catalyst **57** and by catalyst **53b** revealed a considerable difference between the values of k_i/k_p obtained in each case. For the ROMP of **30xa** by **57**, k_i/k_p is 4.35 as compared with 0.056 (in CDCl_3) or 0.96 (in CD_2Cl_2) for **53b**. This difference is attributed in part to an enhanced rate of initiation in the case of **57** and to a decreased rate of propagation. These two factors combine to afford increased control over the system. ROMP of **30xa** by **57** gives a polymer with a polydispersity index as low as 1.05 depending on the conditions used ($[\text{M}_0]/[\text{I}_0] = 100/1$ in CH_2Cl_2 , 4 h at room temperature). It is believed that the modification of the phosphine ligands has implications in terms of both steric and electronic effects, with the silyl-substituted phosphine being slightly less basic and having a slightly smaller cone angle than its tricyclohexyl counterpart.



Detailed analysis of the mechanism of (phosphine)ruthenium-alkylidene-catalyzed metathesis [97] has recently led to elegant *in situ* modifications of the catalyst [98], and a significant improvement in the ROMP performance has been achieved through the addition of phosphines that are smaller and less basic than tricyclohexylphosphine to the reaction mixture. Dissociation of tricyclohexylphosphine produces a 14-electron intermediate, which may then associate either phosphine or monomer, according to Scheme 3.2-34. Comparison of the rate of association of phosphine versus that of olefin demonstrates that the former is significantly higher, with the k_{-1}/k_2 ratio taking values of 1.3×10^4 for the reaction of the model compound ethyl vinyl ether with catalyst **53b** and 2.6×10^6 for the corresponding diiodo derivative [97]. Because phosphine exchange is fast compared to association of the olefin, it can be deduced that the equilibrium between

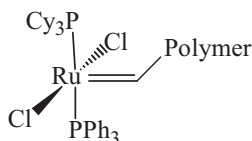


Scheme 3.2-34. Dissociative ligand exchange monomer/phosphine.



Scheme 3.2-35. Modification of ruthenium alkylidenes via in-situ phosphine exchange.

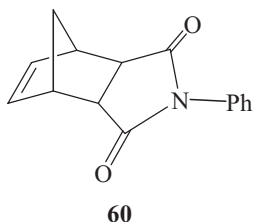
the bis(tricyclohexylphosphine) species, **53b**, and the mixed phosphine species, **58**, is established prior to initiation (Scheme 3.2-35).



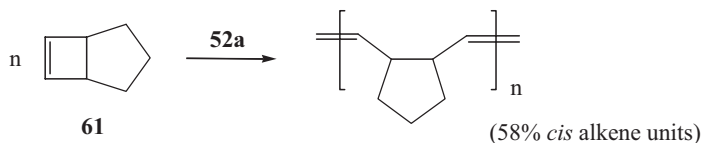
59

The addition of an aryl phosphine to the reaction mixture brings about a decrease in both the rate constant for initiation, k_i , and the rate constant for propagation, k_p . However, the added phosphine binds less strongly to the phenyl-substituted alkylidene, **58**, than to the alkylidenes bearing the growing polymer chain, **59**. Thus, the relative values of k_i and k_p are favorably affected (in terms of achieving living polymerization) in that the ratio k_i/k_p increases. In the case of ROMP of **60** using catalyst **53b**, k_i/k_p increases from 0.73 to 2.43 when 1 equivalent of triphenylphosphine is added and to 10.2 when 5 equivalents of triphenylphosphine are added [98]. In addition, increasing k_i relative to k_p allows for greater control over the system such that the polydispersities of the product polymers are smaller. ROMP of monomer **60** using catalyst **53b** gave a product with a PDI of 1.25, whereas the resultant polymer had a PDI of 1.07 when the polymerization was carried out in the presence of added triphenylphosphine ($[M_0]/[I_0] = 50/1$ in CH_2Cl_2 at 23°C , 5 equivalents of PPh_3). Depending on the conditions used in the ROMP of this monomer employing **53b** with added triphenylphosphine, PDIs as low as 1.04 were obtained ($[M_0]/[I_0] = 250/1$ in CH_2Cl_2 at 23°C , 1 equivalent of PPh_3). Comparison with the k_i/k_p data in Table 3.2-2 suggests that the unmodified polymerization system of **60** and catalyst **53b** could be affected by a small amount of secondary metathesis, and the rates of secondary reactions are significantly

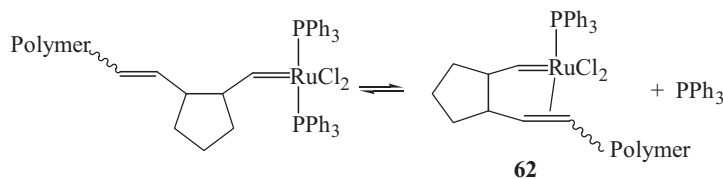
reduced upon addition of PPh_3 . Thus, it was demonstrated that a more controlled polymerization could be achieved via the addition of alternative phosphines, resulting in the formation of nearly monodisperse polymers.



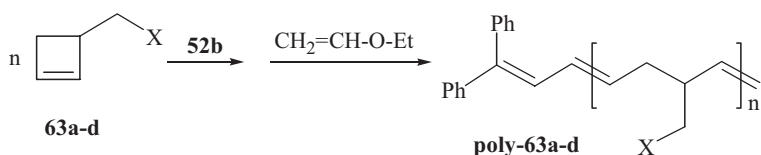
Monomers containing unsaturated 4- and 8-membered ring structures and their polymerization behavior Complex **52a** is sufficiently active for catalyzing the controlled polymerization of highly strained cyclic olefins that contain 4-membered ring structures. Both bicyclo[3.2.0]hept-6-ene, **61**, (Scheme 3.2-36) [99a] and bicyclo[4.2.0]oct-7-ene [99b] are converted into polymers with a PDI of 1.2. For the polymerization of these monomers, a linear relationship exists between M_n and the mole ratio of monomer to catalyst. These polymerizations are well controlled and do not require additional phosphine. ^{31}P NMR analysis of the polymerization mixture of bicycloheptene monomer **61** and catalyst **52a** reveals resonances at δ -4.9 , 29.2 , and 41.7 ppm. These signals are assigned to free triphenylphosphine and two different ruthenium-alkylidene species, one that bears one phosphine ligand (δ 41.7) and a second one that contains two phosphine ligands (δ 29.2). It has been proposed that monophosphine adduct **62** is formed, which is stabilized by chelation with the double bond on the growing polymer chain adjacent to the metal-carbene bond (Scheme 3.2-37). This intramolecular olefin coordination has been suggested to reduce the rate of chain propagation, thereby increasing k_i/k_p . The k_i/k_p ratio of 0.15 is higher than that determined for ROMP of norbornene with **52a** and gives rise to a relatively well-controlled polymerization system.



Scheme 3.2-36. ROMP of bicyclo[3.2.0]hept-6-ene.



Scheme 3.2-37. Intramolecular chelation during chain propagation of bicyclic olefin **62**.



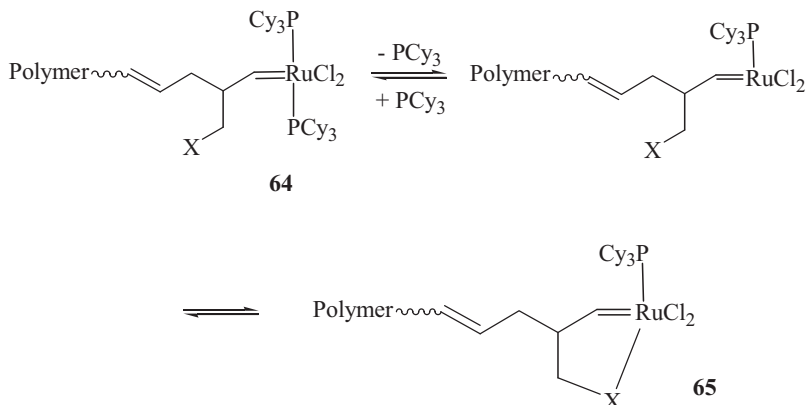
63a: X = OCH₂Ph

63b: X = OPh₃

63c: X = OC(O)Ph

63d: X = NⁱPr₂

Scheme 3.2-38. Polymerization of functionalized cyclobutene derivatives.



Scheme 3.2-39. Chelation during polymerization of functionalized cyclobutenes.

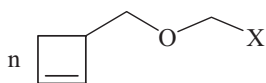
Similarly, chelate structures are formed during the polymerization of 3-substituted cyclobutenes **63a–d** with catalyst **52b** (Scheme 3.2-38), and they determine whether the polymerization is living or nonliving [100].

The functional group X of the repeating unit attached to the chain-propagating metal center is in the right position to form a 5-membered ring chelate structure, **65** (Scheme 3.2-39). Coordination of X increases in the order of –OC(O)Ph (benzoyloxy) < –OCPh₃ (trityloxy) < –OCH₂Ph (benzyloxy) < –N(ⁱPr)₂ (diisopropylamino) and reduces the rate of chain propagation. Approximately 200 equivalents of monomer are consumed within less than 0.5 h at 45 °C in the case of monomers **63b** and **63c**. This compares with a reaction time of 1.0–1.5 h for the reaction of 150 equivalents of cyclobutene derivative **63a**. The increase in reaction time can be correlated with the ratio of the monophosphine species **65** to bisphosphine species **64** formed during chain propagation, and the product polydispersity decreases with increasing ratio of **65/64** [100].

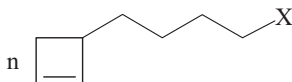
The relative amounts of **64** and **65** are determined by ¹H NMR spectroscopy, as they give rise to two characteristic alkylidene resonances at δ 19.8–19.9 (toluene –d₈), corresponding to **64**, and δ 17.7–18.4, assigned to **65**. The ratio of **65/64** decreases from 8.9 to 1.4 to 0.57 for X = –OCH₂Ph, –OCPh₃, and –OC(O)Ph,

respectively. The polymerization of the benzyl-ether-based monomer **63a** is living. The resulting $\text{PhCH}_2\text{OCH}_2$ -functionalized 1,4-polybutadiene, **poly-63a**, has M_w/M_n values between 1.15 and 1.18 when monomer:catalyst ratios ranging from 26:1 to 152:1 are used (catalyst **52b**, 1.0–1.5 h at 45 °C, in toluene) [100]. However, the molar mass distributions of polymers obtained from the other two cyclobutene derivatives **63b,c** are significantly higher. The M_w/M_n values range from 1.44 to 1.30 for **poly-63b** prepared using 52–189 equivalents of monomer, and M_w/M_n is between 1.70 and 1.57 for **poly-63c** prepared from 26–218 equivalents of **63c** and catalyst **52b**. The dialkylamino-functionalized cyclobutene derivative **63d** requires more than 4.5 h at 45 °C for the polymerization of a comparable number of equivalents of monomer. Products with low M_w/M_n values of 1.13 and 1.25 are obtained, but a small amount of catalyst decomposition is observed during these prolonged reaction times.

Monomers **63e–g** contain an ether-functionalized spacer between the cyclobutene ring and functionality X. The ratio k_i/k_p increases; however, chelation is quite pronounced, and the rate of propagation is so much reduced that catalyst decomposition pathways begin to interfere with polymerization [100].

**63e–g****63e:** X = CO_2Me **63f:** X = $\text{C}(\text{O})\text{NMe}_2$ **63g:** X = $\text{C}(\text{O})\text{N}(\text{i-Pr})_2$

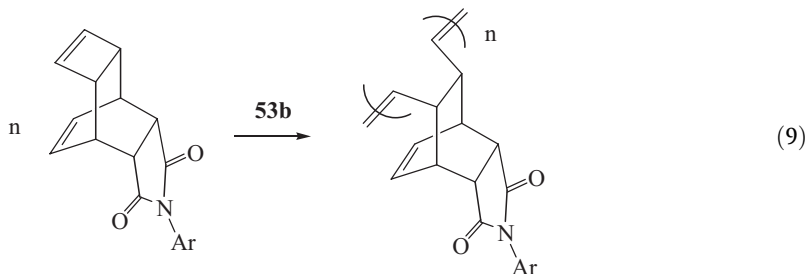
Living polymerization results can be achieved for the benzoyloxy-functionalized cyclobutene derivative **63c** by using the benzylidene-ruthenium catalyst **53b**. The rate of initiation is significantly increased, and **poly-63c** with M_n of 29,500 and M_w/M_n of 1.22 is obtained from a 220:1 ratio of **63c**:**53b**. This compares with M_w/M_n of 1.7 when **52b** is employed as the catalyst.

**66a–d****66a:** X = CH_2OH **66b:** X = CO_2H **66c:** X = CO_2Me **66d:** X = $\text{C}(\text{O})\text{NHBu}$

Other cyclobutene monomers are compounds **66a–d**, which bear hydroxyl, carboxylic acid, and carboxylic acid derivative groups further removed from the monomer double bond [100]. These monomers display a reduced tendency for intramolecular coordination. Reactions of **66a–d** with **53b** carried out for 2 h at 25 °C in THF lead to the formation of well-defined products. Polymers with narrow molar mass distributions, M_w/M_n between 1.11 and 1.19, are obtained from monomer:catalyst ratios ranging from 25:1 to 161:1. The polydispersity for the polymer formed from acid **66b** does not increase after extending the reaction time to 6 h, and the addition of a second monomer portion, 350 equivalents of **66b**, after 2 h leads to an increase in M_n from 4400 to 53,400, with relatively little broadening of the molar mass distribution. These results confirm the living char-

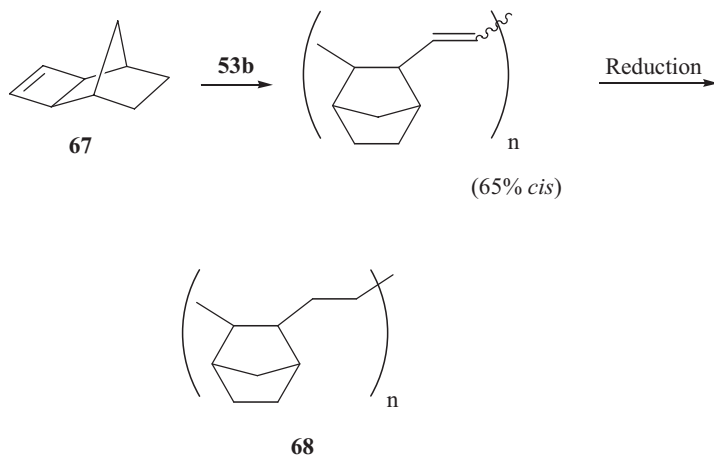
acter of these cyclobutene polymerizations and their remarkable stability in the presence of functional groups that well-defined ruthenium alkylidenes exhibit.

Aryl-substituted dicarboximides of *endo*-tricyclo[4.2.2.0^{2,5}]deca-3,9-diene have been submitted to living ROMP catalyzed by **53b** (Eq. (9)). The resulting products display narrow molar mass distributions with M_w/M_n values between 1.07 and 1.13 (polymerization conditions: 100–200 equivalents of monomer, 5 h at 25 °C) [101]. By comparison, polymerizations with molybdenum alkylidenes **19d** and **19f** were reported to proceed in a less-controlled manner, and polymers with broader molar mass distributions were obtained.



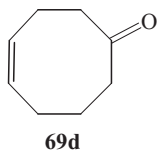
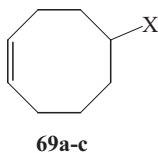
Ar: Ph, 2-F-Ph, C₆F₅, 2-CF₃-Ph, 4-MeO-Ph, 2-t-Bu-Ph, 2-CF₃O-Ph

Exo-tricyclo[4.2.1.0^{2,5}]non-3-ene, **67**, can serve as a monomer in living metathesis polymerizations with the tricyclohexylphosphine-based catalyst **53b**. A strictly alternating ethylene-norbornene copolymer, **68**, with a narrow molar mass distribution, $M_n = 46,000$ and $M_w/M_n = 1.13$, is obtained from ROMP of tricyclic olefin **67** (150 equivalents of monomer, 4 h at 40 °C) and subsequent reduction of the polymer double bonds (Scheme 3.2-40) [102]. This polymer is slightly enriched in syndiotactic units (70% *r* diads), which contrasts with the atactic to isotactic stereochemistry usually obtained in metallocene-catalyzed.



Scheme 3.2-40. Strictly alternating ethylene-norbornene copolymers via living ROMP.

Ruthenium alkylidene **52b** has been successfully employed in the polymerization of less-strained, functionalized cyclooctene derivatives **69a–d**. Overall, good polymer yields are obtained from 1000:1 monomer:catalyst ratios after 24–144 h at 23 °C. However, these are nonliving polymerizations, and the resulting ring-opened polycyclooctenes display relatively high polydispersities between 1.6 and 1.9 [103].



69a: X = OH

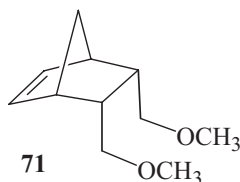
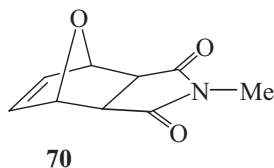
69b: X = Br

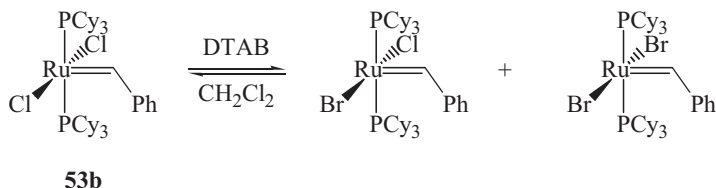
69c: X = OC(O)CH₃

Initial results indicate that polymerizations of cyclooctadiene with catalyst **53b** can be carried out in a controlled manner by adding 2 equivalents of triphenylphosphine to the polymerization mixture. The polymerization is quenched upon addition of ethyl vinyl ether before significant secondary metathesis occurs, and M_w/M_n of 1.2 can be achieved for a polymer with $M_n = 8000$ [98].

Aqueous ROMP The use of water as the solvent for chemical reactions offers many advantages over the use of organic solvents, including that it is widely available, inexpensive, and (perhaps of greatest significance) nontoxic [104]. Conventional ruthenium catalysts have been shown to be capable of catalyzing the aqueous ROMP of strained cyclic olefins [38]. However, the propagating species has never been observed, and these polymerizations are not living. The ruthenium-based metathesis catalysts, **52a,b** and **53a,b**, are stable in organic solution in the absence and also in the presence of aqueous and other protic polar solvents. This property prompted the investigation of their activity in the ROMP of strained cyclic olefins in aqueous media [105].

Complexes **52b** and **53b** were found to catalyze the living ROMP of functionalized norbornenes and 7-oxanorbornenes in aqueous suspensions and emulsions. A surfactant such as dodecyltrimethylammonium bromide or chloride is added to the reaction mixture for polymerizations to be carried out in emulsion. Both hydrophilic and hydrophobic monomers such as 7-oxanorbornadiene dicarboximide **70** and *endo*-norbornene derivative **71**, respectively, are effectively polymerized with catalyst **53b** in suspension and emulsion. These are living polymerizations, and products with narrow molar mass distributions, M_w/M_n between 1.07 and 1.19, are obtained for reactions performed with monomer:catalyst ratios between 100:1 and 159:1.





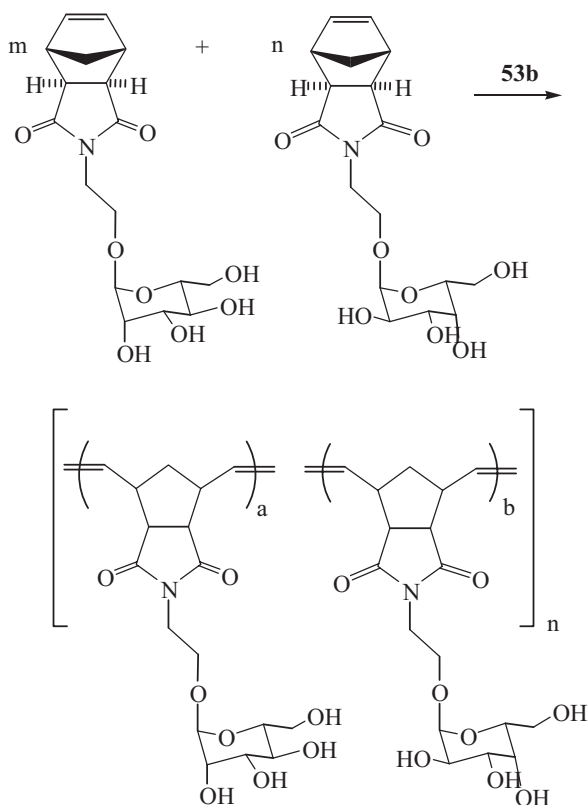
Scheme 3.2-41. Ligand scrambling in the presence of the surfactant dodecyltrimethylammonium bromide, DTAB.

In emulsion systems employing the bromide-based tetraalkylammonium surfactant DTAB, the rate of polymerization is lower than in solution polymerizations. This can lead to slightly increased polydispersities or bimodal distributions when polymerizations are allowed to proceed to complete monomer conversions, as secondary reactions can begin to interfere after extended reaction times. The reduced rate of polymerization is believed to be due to the presence of less active polymerization catalysts that bear bromide ligands [106a]. Mixtures of ruthenium-alkylidene complexes containing bromide, mixed chloride and bromide, and chloride ligands are formed in exchange reactions between metathesis catalyst **53b** and the bromide anion of the surfactant (Scheme 3.2-41). However, the good polymerization activities of **52b** and **53b** should be preserved when using, for example, dodecyltrimethylammonium chloride.

Catalyst **53b** in combination with the surfactants sodium dodecyl sulfate or Dowfax 3B2 has been employed recently in the preparation of polymer latexes from cyclooctadiene and cyclooctene [107]. The resulting polymers have relatively broad molar mass distributions with PDIs between 1.5 and 1.6 and do not appear to be living systems. Furthermore, norbornene polymerizations performed in aqueous emulsions have been reported that result in the formation of latexes [107]. The active ruthenium-based catalyst is generated *in situ* from bis(TPPTS)-ruthenium dichloride (TPPTS = tris(3-sulfonatophenyl)phosphine, sodium salt) and ethyl diazoacetate. This is a two-component catalyst system, which is suitable for the generation of latexes, but the identity of the catalyst structure has not yet been clearly characterized, and the products reported seem to display very high molar masses with unspecified polydispersities.

Polymerization systems that allow polymerization in protic or aqueous media can be very useful when monomers or polymers display limited solubility in common organic solvents or when the desired products are to be used in biomedical studies or therapeutical applications. For example, investigations into developing an understanding of biological receptor/ligand binding and, e.g., receptor clustering for activating signaling pathways, have employed Ru-catalyzed ROMP [108]. Well-defined, physiologically active polymers containing multiple copies of carbohydrate units attached to a polymer main chain have been synthesized by olefin metathesis in protic organic and aqueous media. Scheme 3.2-42 displays an example of a copolymer synthesis in which the product contains mannose and galactose side chains attached to a poly(norbornenedicarboximide)-type backbone [108a].

ROMP employing emulsion conditions has been used for the preparation of disulfated neoglycopolymer **72** [108b]. This polymer was found to act as a multi-



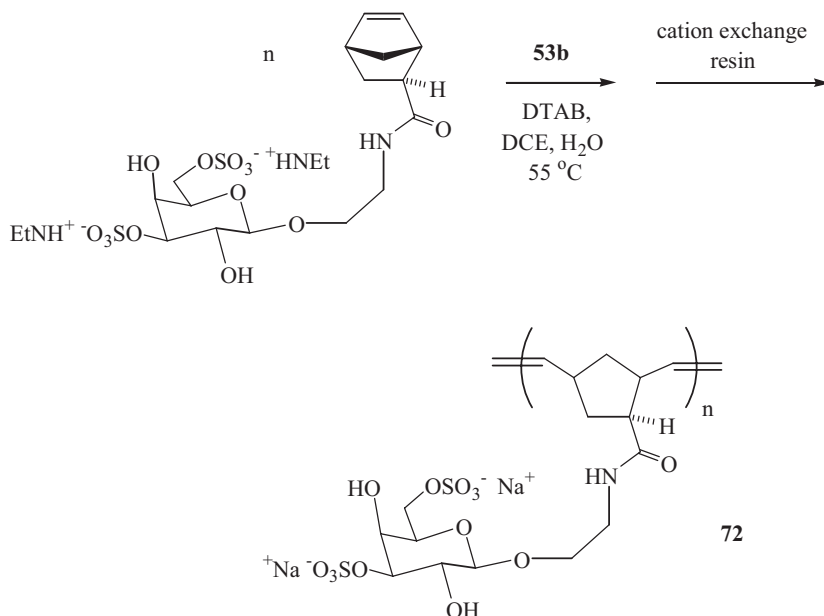
Scheme 3.2-42. Ru-catalyzed ROMP for the preparation of physiologically active copolymers containing mannose and galactose sidechains.

valent ligand that was approximately 500-fold more effective than the monovalent inhibitor sLe^x at blocking P-selectin-cell interactions.

Additional work on living ROMP of carbohydrate-substituted monomers has been published recently [109].

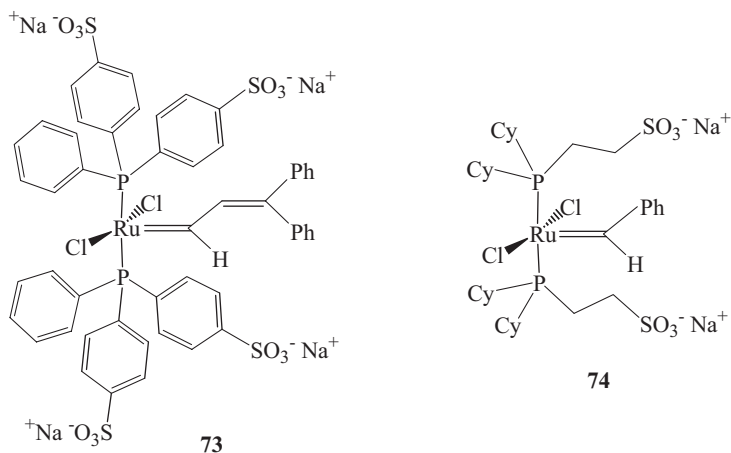
In the aqueous ROMP systems described above, it is necessary to dissolve the catalyst in a small amount of an organic solvent (dichloromethane or 1,2-dichloroethane) prior to its introduction into the reaction mixture due to its poor solubility in water. Thus, these polymerizations were not entirely aqueous, and it is probable that most of the reaction occurs in the organic phase, albeit proportionately small in volume. They did, however, testify to the stability and activity of these complexes in the presence of water and to the living character of the polymerization.

This subsequently led to the development of water-soluble ruthenium-based catalysts, which could be used to initiate ROMP in entirely aqueous systems. Water solubility was achieved by the modification of the phosphine ligands to produce complexes such as **75** and **76**, which catalyze the ROMP of strained cyclic olefins in water [110]. Initial studies into designing water-soluble metathesis catalysts

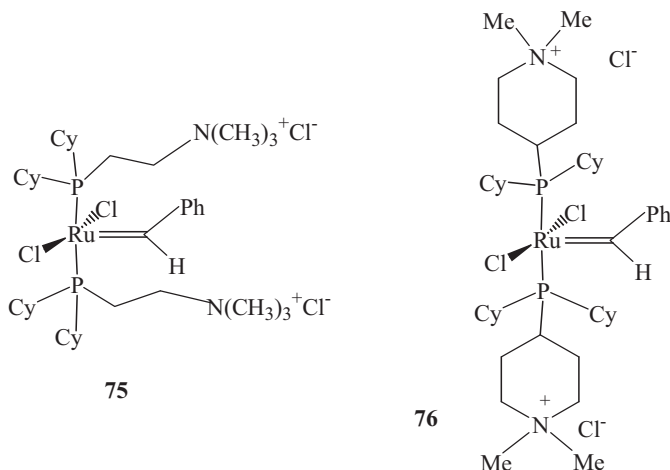


Scheme 3.2-43. ROMP in emulsion for the preparation of a sulfated neoglycopolymer which is a selective P-selectin inhibitor.

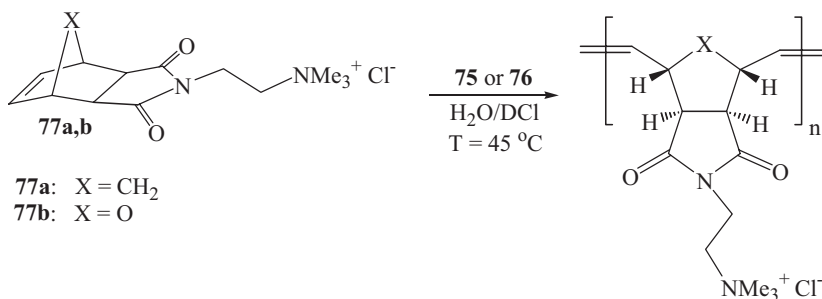
included the preparation of ruthenium alkylidene **73**, employing the commercially available bis(sulfonate) ligand $\text{PhP}(p\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_2$. While complex **73** was water soluble, it did not initiate metathesis polymerization in aqueous solution [106a]. This lack of activity could be due to the poor electron-donating character of the sulfonate-substituted triarylphosphine or to the relatively small cone angle. Another ruthenium-alkylidene compound, **74**, could be synthesized in solution but was found to be too unstable to allow its isolation [106a].



Complexes **75** and **76** were isolated as solids [106, 110] and an X-ray crystal structure was obtained from **75** [106a]. Both alkylidene compounds are completely soluble in dichloromethane, water, and methanol but are very poorly soluble in many other common organic solvents such as benzene, THF, acetone, and ethanol. They are air sensitive in solution, and standard inert gas techniques are employed. Both compounds **75** and **76** are metathesis active; however, initial polymerizations were not living due to decomposition of the propagating species [106]. The polydispersities for the polymers resulting from **77a,b** were relatively high, PDI \sim 2.3, and the product molar masses were lower than anticipated, as monomer conversions ranged from 45–80%. Decomposition is believed to be promoted by the small amount of hydroxide ions that are present in neutral aqueous solutions, and catalyst decomposition is significantly accelerated upon addition of aqueous NaOD.



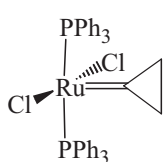
Living ROMP is achieved upon addition of a Brønsted acid such as DCl (0.3–1.0 equivalent relative to the catalyst), which corroborates the above explanation [106]. Addition of the acid also accelerates the polymerization by approximately 1 order of magnitude. These reactions of **75**, **76** with DCl and subsequent polymerizations of cycloolefin monomers in aqueous media can be monitored by NMR spectroscopy. Two ruthenium-alkylidene species are detected upon addition of DCl to **75**. These are the original alkylidene **75**, with an alkylidene proton signal at δ 19.76 ppm (singlet), and a new ruthenium-alkylidene compound, δ 20.12 ppm (d, J_{PH} = 12.0 Hz). The latter compound has been proposed to contain a molecule of coordinated H_2O that has replaced one of the phosphine ligands in **75**. The living nature of these DCl-modified aqueous systems (Scheme 3.2-44) has been proven by demonstrating the absence of chain transfer and termination using 1H NMR spectroscopy and by isolating a polymer with a low polydispersity index from the reaction of cyclic olefin **77a** (polymerization at 45 °C, M_n = 11,500, PDI = 1.24). The propagating ruthenium alkylidene could be directly observed via 1H NMR,



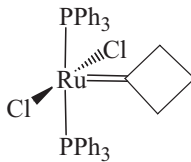
Scheme 3.2-44. Aqueous ROMP of ionic norbornene and 7-oxanorbornene derivatives.

which has previously not been possible for conventional aqueous ROMP systems. At 45 °C, a broad coalesced resonance at 19.2 ppm was detected for the two types of chain-propagating alkylidenes, which are in a rapid equilibrium via phosphine scrambling. The intensity of the alkylidene resonance did not decrease during chain propagation or after all of the monomer had been consumed (after 15 min at 45 °C, the polymerization was >95% complete). Furthermore, block copolymer synthesis has been successfully carried out in aqueous solution (from **77a** and **77b**.) Other monomers that have been reported to undergo living ROMP with **75** and **76** include 7-oxanorbornene derivative **70** and *exo,exo*-5,6-dimethoxymethyl-7-oxanorbornene.

Modified ruthenium-alkylidene catalysts Selected variants of complex **53a** have been prepared by modifying the structure of the carbene. Both compounds **78** and **79** [111] catalyze the living ROMP of norbornene. However, α -heteroatom substituents have been found to generally reduce the ROMP activity of Ru-alkylidene complexes significantly when compared with carbon-based substituents.



78

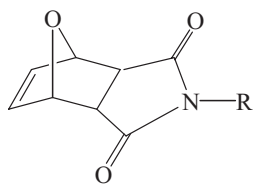
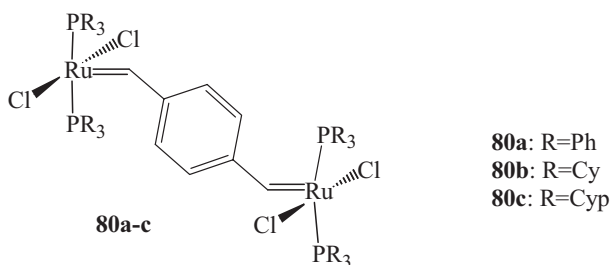


79

Other complexes based on Grubbs catalysts have been subsequently developed that are capable of catalyzing the living ROMP of selected monomers. Among these are a series of bimetallic ruthenium catalysts **80a–c** [112], which allow polymer chain growth to proceed simultaneously from both alkylidene units. They are suitable for syntheses of ABA-type triblock copolymers that require only two successive monomer additions to the catalyst, initially forming the center block B and subsequently both A blocks upon addition of the second monomer.

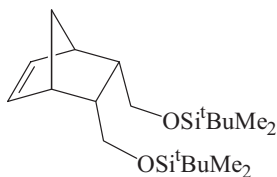
With regard to their relative activities in the catalysis of ROMP, these complexes behave in a similar manner to their mononuclear analogues **53a** and **53b**. Complex **80a** catalyzes the living ROMP of norbornene, but does not polymerize functionalized norbornenes or 7-oxanorbornenes. The opposite is true for **80b** and **80c**, which are more active and catalyze the living ROMP of the latter monomers, but chain-transfer and backbiting reactions take place during the ROMP of norbornene.

For example, catalyst **80a** has been found to be inactive in the polymerization of monomers **70**, **81**, and **56**, while the living ROMP of these monomers has been achieved using catalysts **80b** and **80c**. The living nature of these systems, as evidenced by the existence of a linear relationship between M_n and $[M]/[C]$, has been confirmed by the successful preparation of block copolymers of **56** and **70/45**.



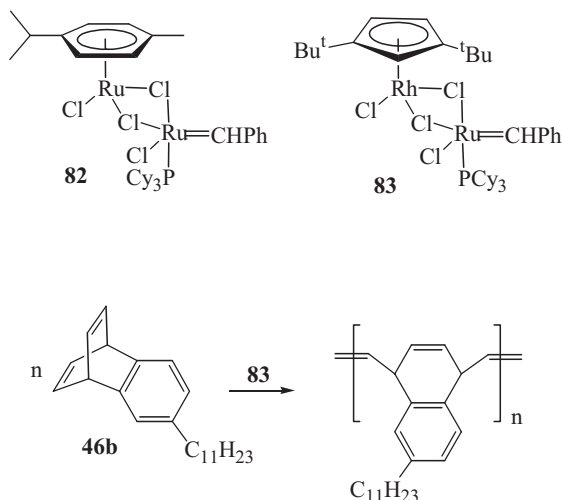
70: R = Me

81: R = C₈H₁₇



56

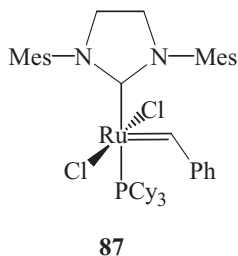
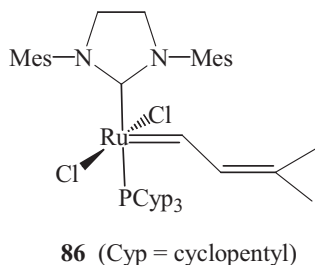
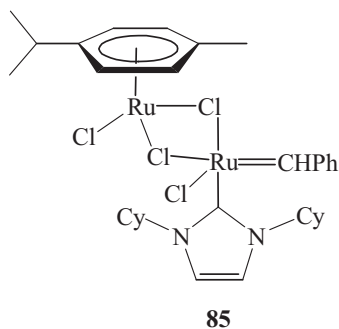
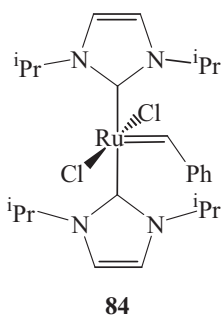
Alkylidene compound **82** represents another example of a homobimetallic ruthenium catalyst for olefin metathesis [113]. However, this type of ROMP system has not yet been fine-tuned toward living polymerization behavior. It is currently assumed that chain growth is predominantly or solely initiated by the ruthenium center that bears the alkylidene unit of **82**. The activity of **82** for cyclooctadiene polymerization is approximately twice as high as that of catalyst **53b**. The activity is further increased by a factor of 3 (with respect to the activity of **82**) when the $(\eta^6\text{-aryl})\text{Ru}$ unit is replaced by an $(\eta^5\text{-di-}i\text{-tert-butylcyclopentadienyl})\text{Rh}$ moiety to give heterobimetallic catalyst **83** [113]. This catalyst is sufficiently active to polymerize



Scheme 3.2-45. ROMP of benzobarrelene derivative **46b**.

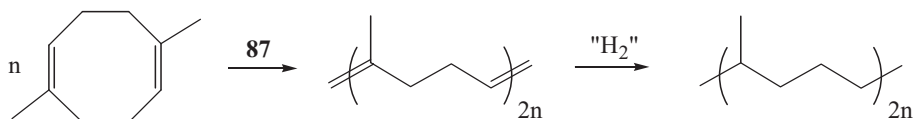
benzobarrelene **46b** (Scheme 3.2-45) and bis(trifluoromethyl)norbornadiene **21** at a sufficiently high rate that catalyst decomposition does not interfere. It has not yet been established whether polymerizations with **83** can be performed in a living manner.

A recent phase of catalyst design is constituted by the development of *N*-heterocyclic carbene ligands, which are relatively easy to prepare and modify [11b, 114]. This allows for the tuning of the properties of the complex through control over the steric and electronic properties of the ligand. These complexes show increased metathesis activity and stability to air, moisture, and temperature when compared to catalyst **53b**. Their activity has been found to exceed that of existing ruthenium-based catalysts and even of the imido molybdenum-alkylidene catalysts in some cases [115]. Ruthenium-alkylidene complex **84** bearing two *N*-heterocyclic carbene ligands has been found to polymerize a series of functionalized 5-substituted norbornene derivatives [116]. However, the molar mass distributions reported are relatively broad and do not correspond to living polymerization systems. Selected examples of other, mono-*N*-heterocyclic carbene-based Ru complexes have so far proven to be capable of initiating the living ROMP of certain monomers. For example, complex **85**, which is structurally similar to bis(ruthenium) compound **82**, catalyzes the living ROMP of norbornadiene-2,3-dicarboxylic ester **18**, giving a product polymer with a polydispersity of 1.1 [116]. However, the latest *N*-heterocyclic carbene complexes, e.g., **86** and **87** bearing a 2,3-dihydroimidazolyldiene ligand, are often too active for living ROMP, as the growing polymer chain will undergo secondary metathesis reactions [115], and this feature can be specifically employed for the synthesis of telechelics via ROMP [117].

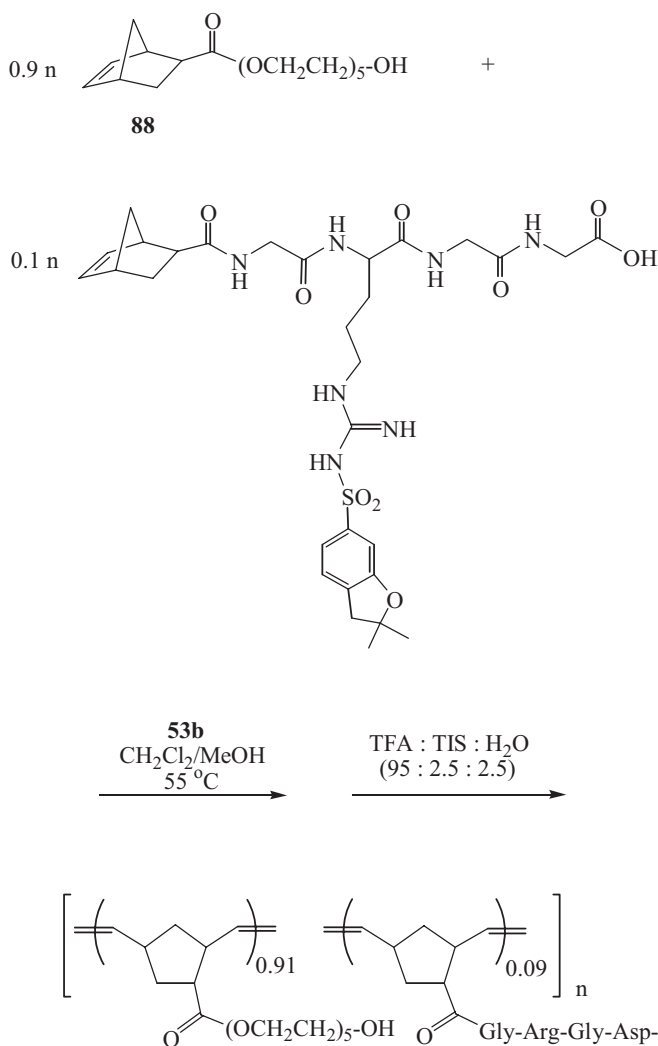


Ru complex **87** is able to catalyze the ROMP of 1,5-dimethyl-1,5-cyclooctadiene, which has previously not been achieved. After 24 h at 55 °C and employing a 1000:1 monomer:catalyst ratio, a regular, 1,4-enchained polyisoprene is obtained in 90% yield with $M_n = 10,000$ and $M_w/M_n = 2.3$ (Scheme 3.2-46) [115]. Subsequent hydrogenation affords an ethylene-propylene copolymer. The molar mass is significantly lower than expected for a living system, and the broad molar mass distribution indicates that a substantial amount of chain transfer has occurred.

Norbornene monomers containing the complex and bulky peptide sequences arginine-glycine-aspartic acid (RGD) and proline-histidine-serine-arginine-asparagine (PHSRN) require catalysts with an exceptionally high activity for ROMP. Initial studies have shown that catalyst **53b** is capable of producing a copolymer that contains 9 mol% of glycine-arginine-glycine-aspartic acid (GRGD)-substituted norbornene, and the predominant fraction of repeating units (91%) is based on EO₅-substituted norbornene **88** (Scheme 3.2-47) [118a]. However, attempts to prepare copolymers that contain larger quantities of the peptide-substituted monomer have resulted in low polymer yields and bimodal mass distributions when **53b** is used for ROMP. By comparison, ruthenium alkylidenes **86**



Scheme 3.2-46. Synthesis of an ethylene-propylene copolymer via ROMP.



Scheme 3.2-47. Polynorbornene copolymers with peptide (GRGD) side chains.

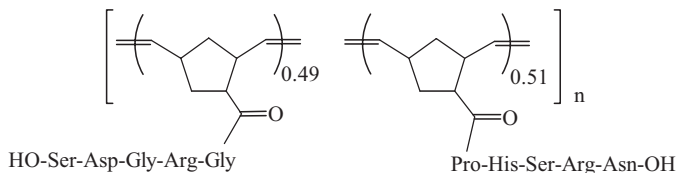
and **87** display outstanding ROMP activities, and larger quantities of the peptide-based monomers can be incorporated into these biomedically interesting copolymers and the corresponding homopolymers can be synthesized [118b]. These polymerizations are carried out in 1:1 solvent mixtures of CH_2Cl_2 and MeOH. Between 10 and 20 equivalents of the monomers are placed into a sealed vial and reacted for 2 h at 55°C . Several of these homo- and copolymerizations proceed in a well-controlled manner, and good yields of polymers with comparatively low polydispersities, M_w/M_n between 1.13 and 1.32, can be obtained.

A polynorbornene containing a 1:1 ratio of GRGDS and PHSRN side chains, **89** (Scheme 3.2-48), exhibits significant biological activity with respect to binding to cell surface integrins. This type of polymer is a potent inhibitor of human fore-



$\text{R}^1 = \text{Gly-Arg(Pbf)-Gly-Asp(O}^t\text{Bu)-Ser(O}^t\text{Bu)-OH}$

$\text{R}^2 = \text{Pro-His(Trt)-Ser(Trt)-Arg(Pbf)-Asn(Trt)-OH}$



89

Scheme 3.2-48. Ru-catalyzed ROMP for the preparation of physiologically active oligopeptide-substituted copolymers.

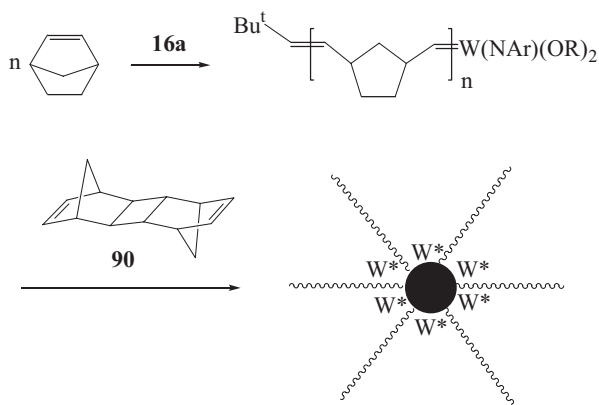
skin fibroblast cell adhesion to fibronectin-coated surfaces. An IC_{50} value of 0.04 ± 0.01 mM has been determined for GRGDS/PHSRN copolymer **89**, which corresponds to a biological activity that is approximately 40 times higher than that for the free GRGDS peptide. This class of polymers is potentially useful in cancer therapy.

3.2.4.9

Star-Shaped Polymers via ROMP

Several synthetic methodologies can be employed for the preparation of star-shaped polymers. These include the use of multifunctional initiators or multifunctional end-capping reagents, as described in Chapters 4.1 and 4.6 (Scheme 3.2-32), respectively. A novel, elegant method is based on the synthesis of a living polymer and subsequent multiple linking of the living chain ends via reaction with a small amount of difunctional or multifunctional monomer [119]. The latter reaction with the di- or multifunctional monomer generates the core of the star. Early examples of this methodology involve the anionic polymerization of styrene followed by reaction with divinylbenzene [12a, 120].

ROMP chemistry, in particular with functional-group-tolerant catalysts, offers the potential to generate very diverse star-shaped polymer compositions. In initial investigations, Bazan and Schrock employed tungsten alkylidene **16a** as the ROMP catalyst and pentacyclic diolefin **90** as a difunctional monomer for generating a star-shaped polynorbornene [119a]. Living polynorbornene with tungsten-alkylidene end groups was prepared, followed by the addition of a few equivalents of diolefin **90** to link up the living chain ends, thus forming the core of the star-shaped polymer (Scheme 3.2-49). An apparent molar mass increase by a factor of



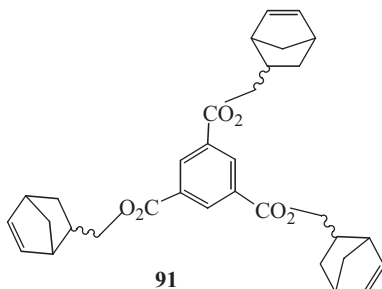
Scheme 3.2-49. Star-shaped polynorbornene via W-catalyzed ROMP.

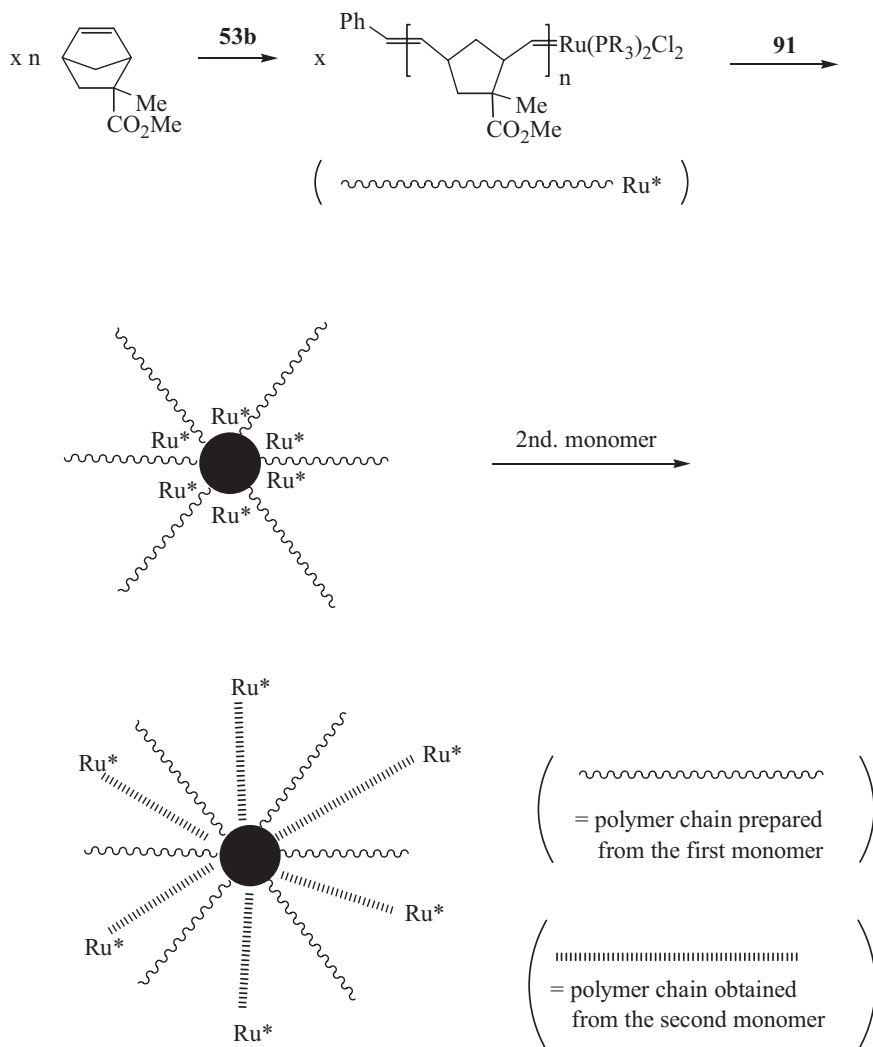
10 is recorded via GPC after the reaction with 4 equivalents of the diolefin, and the molar mass distribution remains relatively narrow, with $M_w/M_n = 1.24$.

The polymerization-active sites remain intact after the formation of the core of the star polymer, and subsequent addition of a second cycloolefin monomer can lead to the formation of a star polymer that contains two different types of arms. These heteroarm star polymers, also called miktoarm star polymers, represent an interesting class of macromolecular architectures [12a].

An early example of a ROMP-based heteroarm star polymer has been reported in which molybdenum catalyst **19a** serves as the polymerization catalyst [119a]. A star-shaped polymer containing poly(2-cyano-5-norbornene) arms is obtained upon reaction of the living ROMP polymer with diolefin **90**. Subsequent addition of 2,3-bis(trifluoromethyl)norbornadiene, **21**, leads to resumption of polymer chain growth. The living star serves as a multifunctional initiator for the polymerization of the second monomer, **21**, and several new polymer arms are formed that grow from the core of the star.

It is useful to achieve fast initiation rates in each of the steps – core formation of the star and initiation of chain growth for the second series of arms – in order to obtain a homogenous composition of the heteroarm stars. In molybdenum-alkylidene-initiated ROMP polymerizations, a relatively unreactive monomer pair has been used for the preparation of the different arms.





Scheme 3.2-50. Hetero arm star polymers via Ru-catalyzed ROMP.

Conner and Heddrick et al. have achieved the synthesis of heteroarm star polymers, employing the highly functional-group-tolerant ruthenium alkylidene **53b** as the ROMP catalyst and trifunctional olefin **91** as the core-forming reagent (Scheme 3.2-50) [119c]. This combination of star topology and narrow molar mass distribution provides access to novel macromolecules with a narrow distribution of three-dimensional sizes. These polymers are promising candidates of pore-forming agents for low dielectric materials, which may find future uses in advanced micro-electronic applications.

References

- 1 (a) SZWARC, M. *Nature* **1956**, 178, 1168.
(b) SZWARC, M.; LEVY, M.; MILKOVICH, M. J. *Am. Chem. Soc.* **1956**, 78, 2656.
(c) SZWARC, M. *Adv. Polym. Sci.* **1983**, 49, 1.
- 2 (a) ZIEGLER, K.; BÄHR, K. *Chem. Ber.* **1928**, 61, 253. (b) ZIEGLER, K.; DERSCH, F.; WOLLTHAN, H. *Justus Liebigs Ann. Chem.* **1934**, 511, 13.
(c) ZIEGLER, K.; JAKOB, L. *Justus Liebigs Ann. Chem.* **1934**, 511, 45.
- 3 (a) ROBERTSON, R. E.; MARION, L. *Can. J. Research* **1948**, 26B, 657.
(b) SANDERSON, J. J.; HAUSER, J. *Am. Chem. Soc.* **1949**, 71, 1595. (c) FLORY, P. J. *Principles of Polymer Chemistry*, Cornell University Press, Ithaca, 1953.
- 4 SCOTT, N. D.; WALKER, J. F.; HANSLEY, V. L. *J. Am. Chem. Soc.* **1936**, 58, 2442.
(b) PAUL, D. E.; LIPKIN, D.; WEISSMAN, S. I. *J. Am. Chem. Soc.* **1956**, 78, 116.
- 5 SCHLICK, S.; LEVY, M. J. *Am. Chem. Soc.* **1960**, 64, 883.
- 6 (a) HADJICHRISTIDIS, N.; PITSIKALIS, M.; PISPAS, S.; IATROU, H. *Chem. Rev.* **2001**, 101, 3747. (b) BYWATER, S. in *Encyclopedia of Polymer Science and Engineering*, 3rd ed., Vol. 2, p. 1–43, MARK, H. F.; KROSCSWITZ, H. F. (Eds.), Wiley-Interscience, New York, 1985. (c) JAGUR-GRODZINSKI, J. J. *Polym. Sci., Part A: Polym. Chem.* **2002**, 40, 2116. (d) HIRAO, A.; LOYKULNANT, S.; ISHIZONE, T. *Prog. Polym. Sci.* **2002**, 27, 1399. (e) MORI, H.; HIRAO, A.; NAKAHAMA, S. *Macromolecules* **1994**, 27, 35. (f) YAMAUCHI, K.; LIZOTTE, J. R.; HERCULES, D. M.; VERGNE, M. J.; LONG, T. E. *J. Am. Chem. Soc.* **2002**, 124, 8599.
- 7 (a) WEBSTER, O. W. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, 38, 2855. (b) WEBSTER, O. W. *Science* **1991**, 251, 887. (c) MECERREYES, D.; JEROME, R.; DUBOIS, P. *Adv. Polym. Sci.* **1999**, 147, 1. (d) YASUDA, H.; IHARA, E. *Adv. Polym. Sci.* **1997**, 133, 53. (e) YASUDA, H.; TAMAI, H. *Prog. Polym. Sci.* **1993**, 18, 1097. (f) CONNOR, E. F.; NYCE, G. W.; MYERS, M.; MÖCK, A.; HEDRICK, J. L. *J. Am. Chem. Soc.* **2002**, 124, 914.
(g) COATES, G. W. *J. Chem. Soc., Dalton Trans.* **2002**, 467.
- 8 LIN, C. H.; XIANG, J. S.; MATYJASZEWSKI, K. *Macromolecules* **1993**, 26, 2785. HIGASHIMURA, T.; ISHIHAMA, Y.; SAWAMOTO, M. *Macromolecules* **1993**, 26, 744. SZWARC, M. *Macromol. Rapid Commun.* **1992**, 13, 141.
- 9 (a) MATYJASZEWSKI, K.; XIA, J. H. *Chem. Rev.* **2001**, 101, 2921. (b) KAMIGAITO, M.; ANDO, T.; SAWAMOTO, M. *Chem. Rev.* **2001**, 101, 3689. (c) QIU, J.; CHARLEUX, B.; MATYJASZEWSKI, K. *Prog. Polym. Sci.* **2001**, 26, 2083. (d) GRANEL, C.; DUBOIS, P.; JEROME, R.; TEYSSIE, P. *Macromolecules* **1996**, 29, 8576. (e) PATTEN, T. E.; XIA, J. H.; ABERNATHY, T.; MATYJASZEWSKI, K. *Science* **1996**, 272, 866. (f) VEREGIN, R. P. N.; GEORGES, M. K.; HAMER, G. K.; KAZMAIER, P. M. *Macromolecules* **1995**, 28, 4391.
- 10 (a) DOI, Y.; SUZUKI, S.; SOGA, K. *Macromolecules* **1986**, 19, 2896. (b) SCHMIDT, G. F.; BROOKHART, M. *J. Am. Chem. Soc.* **1985**, 107, 1443. (c) BROOKHART, M.; DESIMONE, J. M.; GRANT, B. E.; TANNER, M. J. *Macromolecules* **1995**, 28, 5378. (d) KILLIAN, C. M.; TEMPEL, D. J.; JOHNSON, L. K.; BROOKHART, M. *J. Am. Chem. Soc.* **1996**, 118, 11664. (e) GOTTFRIED, A. C.; BROOKHART, M. *Macromolecules* **2001**, 34, 1140. (f) SCOLLARD, J. D.; MCCONVILLE, D. H. *J. Am. Chem. Soc.* **1996**, 118, 10008. (g) BAUMANN, R.; DAVIS, R. M.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1997**, 119, 3830. (h) MATSUI, S.; TOHI, Y.; MITANI, M.; SAITO, J.; MAKIO, H.; TANAKA, H.; NITABARU, M.; NAKANO, T.; FUJITA, T. *Chem. Lett.* **1999**, 1065. (i) MITANI, M.; FURUYAMA, R.; MOHRI, J.; SAITO, J.; ISHII, S.; TERAOKA, H.; KASHIWA, N.; FUJITA, T. *J. Am. Chem. Soc.* **2002**, 124, 7888. (j) TSHUVA, E. Y.; GOLDBERG, I.; KOL, M. *J. Am. Chem. Soc.* **2000**, 122, 10706. (k) TIAN, J.; HUSTAD, P. D.; COATES, G. W. *J. Am. Chem. Soc.* **2001**, 123, 5134. (l) COATES, G. W.; HUSTAD, P. D.; REINARTZ, S. *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 2237.

- 11 Reviews on olefin metathesis: (a) TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, 34, 18. (b) BUCHMEISER, M. R. *Chem. Rev.* **2000**, 100, 1565. (c) SCHROCK, R. R. *Tetrahedron* **1999**, 55, 8141. (d) CHOI, S. K.; GAL, Y. S.; JIN, S. H.; KIM, H. K. *Chem. Rev.* **2000**, 100, 1645. (e) BRESLOW, D. S. *Prog. Polym. Sci.* **1993**, 18, 1141. (f) SCHROCK, R. R. *Acc. Chem. Res.* **1990**, 23, 158. (g) GRUBBS, R. H.; TUMAS, W. *Science* **1989**, 243, 907. (h) NOVAK, B. M.; RISSE, W.; GRUBBS, R. H. *Adv. Polym. Sci.* **1992**, 102, 47.
- 12 (a) PITSIKALIS, M.; PISPAS, S.; MAYS, J. W.; HADJICHRISTIDIS, N. *Adv. Polym. Sci.* **1998**, 135, 1. (b) MALMSTROM, E. E.; HAWKER, C. J. *Macromol. Chem. Phys.* **1998**, 199, 923. (c) UHRIG, D.; MAYS, J. W. *Macromolecules* **2002**, 35, 7182. (d) PERCEC, V.; AHN, C. H.; UNGAR, G.; YEARDLEY, D. J. P.; MÖLLER, M.; SHEIKO, S. S. *Nature* **1998**, 391, 161.
- 13 (a) HEDRICK, J. L.; MAGBITANG, T.; CONNOR, E. F.; GLAUSER, T.; VOLKSEN, W.; HAWKER, C. J.; LEE, V. Y.; MILLER, R. D. *Chem. Eur. J.* **2002**, 8, 3308. (b) HEDRICK, J. L.; MILLER, R. D.; HAWKER, C. J.; CARTER, K. R.; VOLKSEN, W.; YOON, D. Y.; TROLLSAS, M. *Adv. Mater.* **1998**, 10, 1049. (c) MILLER, R. D. *Science* **1999**, 286, 421.
- 14 (a) KIM, S. Y.; SHIN, I. L. G.; LEE, Y. M.; CHO, C. S.; SUNG, Y. K. *J. Controlled Release* **1998**, 51, 13. (b) UHRICH, K. E.; CANNIZZARO, S. M.; LANGER, R. S.; SHAKESHEFF, K. M. *Chem. Rev.* **1999**, 99, 3181. (c) BAE, Y. H.; HUH, K. M.; KIM, Y.; PARK, K.-H. *J. Controlled Release* **2000**, 64, 3. (d) ALLEN, C.; MAYSINGER, D.; EISENBERG, A. *Colloids and Surfaces B: Biointerfaces* **1999**, 16, 3. (e) GREF, R.; MINAMITAKE, Y.; PERACCHIA, M. T.; TRUBETSKOY, V.; TORCHILIN, V.; LANGER, R. *Science* **1994**, 263, 1600.
- 15 LENDLEIN, A.; LANGER, R. *Science* **2002**, 296, 1673.
- 16 (a) COWIE, J. M. G. *Polymers: Chemistry & Physics of Modern Materials*, 2nd. ed., Chapman and Hall, New York, USA, 1991. (b) Odian, *Principles of Polymerization*, 3rd. ed., Wiley-Interscience, New York, 1991. (c) FRIED, J. R. *Polymer Science and Technology*, Prentice Hall PTR, Englewood Cliffs (NJ), USA, 1995.
- 17 JENKINS, A. D.; KRATCHOVIL, P.; STEPTO, R. F. T.; SUTER, U. W. – IUPAC Commission on Macromolecular Nomenclature, *Pure Appl. Chem.* **1996**, 68, 2287.
- 18 KREMER, E. O.; LANSING, W. D. *J. Phys. Chem.* **1935**, 39, 153.
- 19 FLORY, P. J. *J. Am. Chem. Soc.* **1940**, 62, 1561.
- 20 (a) ZIEGLER, K.; BREIL, H.; MARTIN, H.; HOLZKAMP, E. US Patent 3,257,332 (filed Nov. 17, 1953, issued 1966) related to K. Ziegler, Belg. Patent 533,362 (May 5, 1955). Chem. Abstr.: (b) ZIEGLER, K.; HOLZKAMP, E.; BREIL, H.; MARTIN, H. *Angew. Chem.* **1955**, 67, 541. (c) NATTA, G. *Angew. Chem.* **1956**, 68, 393. (d) NATTA, G. *Chim. Ind. Milan* **1955**, 37, 888. (e) NATTA, G.; PINO, P.; CORRADINI, P.; DANUSSO, F.; MANTICA, E.; MAZZANTI, G.; MORAGLIO, G. *J. Am. Chem. Soc.* **1955**, 77, 1708.
- 21 Cr-based catalysts: (a) HOGAN, J. P.; BANKS, R. L. US Patent 2,825,721 (filed Jan. 27, 1953, issued 1958) Philipps Petroleum, Chemical Abstracts 52: 8621h (1958). (b) CLARK, A.; HOGAN, J. P.; BANKS, R. L.; LANNING, W. C. *Ind. Eng. Chem.* **1956**, 48, 1152.
- 22 (a) ANDERSON, A. W.; MERCKLING, N. G. (Du Pont) US Patent 2,721,189 (1955), Chem. Abstr. 50: 3008i. (b) ELEUTERIO, H. S. (Du Pont), US Pat. 3,074,918 (Jan 22, 1963), Chem Abstr. 55: 16005h for related German pat. DE 1,072,811 (1960). (c) TRUETT, W. L.; JOHNSON, D. R.; ROBINSON, I. M.; MONTAGUE, B. A. *J. Am. Chem. Soc.* **1960**, 82, 2337.
- 23 (a) STRECK, R. J. *Mol. Catal.* **1988**, 46, 305. (b) SCHNEIDER, W. A.; MÜLLER, M. F. J. *Mol. Catal.* **1988**, 46, 395. (c) STRECK, R. A. *J. Mol. Catal.* **1982**, 15, 3. (d) PARSHALL, G. W.; ITTEL, S. D. *Homogeneous Catalysis*, 2nd. ed., Wiley-Interscience, New York, 1992. (e) STRECK, R.; WEBER, H. US Patent 3,974,092 (1976). (f) KLOSIEWICZ,

- D. W. US Patent 4,400,340 (1983).
 (g) MINCHAK, R. J.; KETTERING, T. J.; KROENCKE, W. J. US Patent 4,380,617 (1983). (h) GOODALL, B. L.; RHODES, L. F. US Patent 4,923,936 (1990).
- 24 (a) CALDERON, N.; OFSTEAD, E. A.; JUDAY, W. A. *J. Polym. Sci. A-1*, **1967**, 5, 2209. (b) CALDERON, N.; CHEN, H. Y.; SCOTT, K. W. *Tetrahedron Lett.* **1967**, 3327. (c) CALDERON, N.; OFSTEAD, E. A.; WARD, J. P.; JUDY, W. A.; SCOTT, K. W. *J. Am. Chem. Soc.* **1968**, 90, 4133.
- 25 MOL, J. C.; MOULIJN, J. A.; BOELHOUWER, C. J. *Chem. Soc., Chem. Commun.* **1968**, 633.
- 26 DALL'ASTA, G.; MOTRONI, D. *Eur. Polym. J.* **1971**, 7, 707.
- 27 (a) BENSON, S. W.; CRUICKSHANK, F. R.; GOLDEN, D. M.; HAUGEN, G. R.; O'NEAL, H. E.; RODGERS, A. S.; SHAW, R.; WALSH, R. *Chem. Rev.* **1969**, 69, 279. (b) SCHLEYER, P. V. R.; WILLIAMS, J. E.; BLANCHARD, K. R. *J. Am. Chem. Soc.* **1970**, 92, 2377.
- 28 (a) LEBEDEV, B.; SMIRNOVA, N. *Macromol. Chem. Phys.* **1994**, 195, 35. (b) LEBEDEV, B.; SMIRNOVA, N.; KIPARISOVA, Y.; MAKOVETSKY, K. *Macromol. Chem. Phys.* **1992**, 193, 1399. (c) KRANZ, D.; BECK, M. *Angew. Makromol. Chem.* **1972**, 27, 29.
- 29 PATTON, P. A.; LILLYA, C. P.; MCCARTHY, T. J. *Macromolecules* **1986**, 19, 1266.
- 30 (a) BANKS, R. L.; BAILEY, G. C. *Ind. Eng. Chem., Prod. Res. Dev.* **1964**, 3, 170. (b) BANKS, R. L. *Chemtech* **1986**, 16, 112.
- 31 (a) IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, USA, 1997. (b) R. H. GRUBBS in *Comprehensive Organometallic Chemistry*, Vol. 8, p. 499, WILKINSON, G. (Ed.), Pergamon, Oxford, 1982.
- 32 NATTA, G.; DALL'ASTA, G.; MAZZANTI, G. *Angew. Chem., Int. Ed. Engl.* **1964**, 3, 723.
- 33 (a) DALL'ASTA, G.; MAZZANTI, G.; NATTA, G.; PORRI, L. *Makromol. Chem.* **1962**, 56, 224. (b) NATTA, G.; DALL'ASTA, G.; MAZZANTI, G.; MOTRONI, G. *Makromol. Chem.* **1963**, 69, 163.
- 34 (a) ZUECH, E. A. *J. Chem. Soc., Chem. Commun.* **1968**, 1182. (b) HUGHES, W. B. *J. Chem. Soc., Chem. Commun.* **1969**, 431. (c) ZUECH, E. A.; HUGHES, W. B.; KUBICEK, D. H.; KITTLEMAN, E. T. *J. Am. Chem. Soc.* **1970**, 92, 528. (d) LARROCHE, C.; LAVAL, J. P.; LATTES, A.; LECONTE, M.; QUIGNARD, F.; BASSET, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 220.
- 35 PAMPUS, G.; LEHNERT, G. *Makromol. Chem.* **1974**, 175, 2605.
- 36 HERISSON, J.-L.; CHAUVIN, Y. *Makromol. Chem.* **1971**, 141, 161.
- 37 (a) SAITO, K.; YAMAGUCHI, T.; TANABE, K.; OGURA, T.; YAGI, M. *Bull. Chem. Soc. Jpn.* **1979**, 52, 3192. (b) MANGO, F. D. US Patent 3,424,811 (1969).
- 38 (a) RINEHART, R. E.; SMITH, H. P. *J. Polym. Sci.* **1965**, B-3, 1049. (b) MICHELOTTI, F. W.; KEAVENEY, J. *Polym. Sci.*, **1965**, A-3, 895. (c) NATTA, D.; DALL'ASTA, PORRI, L. *Makromol. Chem.* **1965**, 81, 253. (d) NOVAK, B. M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1988**, 110, 960. (e) NOVAK, B. M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1988**, 110, 7542.
- 39 (a) SCHROCK, R. R. *J. Organomet. Chem.* **1986**, 300, 249. (b) SCHROCK, R. R. *J. Chem. Soc., Dalton Trans.* **2001**, 2541.
- 40 (a) GRUBBS, R. H.; CARR, D. D.; HOPPIN, C.; BURK, P. L. *J. Am. Chem. Soc.* **1976**, 98, 3478. (b) GRUBBS, R. H.; BURK, P. L.; CARR, D. D. *J. Am. Chem. Soc.* **1975**, 97, 3265. (c) KATZ, T. J.; ROTHCHILD, R. J. *Am. Chem. Soc.* **1976**, 98, 2519. (d) KATZ, T. J.; MCGINNIS, J. *J. Am. Chem. Soc.* **1975**, 97, 1592.
- 41 (a) FISCHER, E. O.; MAASBOL, A. *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 580. (b) CASEY, C. P.; BURKHARDT, T. J. *J. Am. Chem. Soc.* **1973**, 95, 5833. (c) FISCHER, E. O.; DORRER, B. *Chem. Ber.* **1974**, 107, 1156. (d) CASEY, C. P.; BURKHARDT, T. J. *J. Am. Chem. Soc.* **1974**, 96, 7808. (e) CASEY, C. P.; TUINSTRAL, H. E.; SAEMAN, M. C. *J. Am. Chem. Soc.* **1976**, 98, 608.
- 42 KATZ, T. J.; LEE, S. J.; ACTON, N. *Tetrahedron Lett.* **1976**, 4247.
- 43 (a) TEBBE, F. N.; PARSHALL, G. W.; REDDY, G. S. *J. Am. Chem. Soc.*

- 1978, 100, 3611. (b) TEBBE, F. N.; PARSHALL, G. W.; OVENALL, D. W. *J. Am. Chem. Soc.* **1979**, 101, 5074.
- 44 ROCKLAGE, S. M.; FELLMANN, J. D.; RUPPRECHT, G. A.; MESSERLY, L. W.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1981**, 103, 1440.
- 45 WENGROVIUS, J. H.; SCHROCK, R. R.; CHURCHILL, M. R.; MISSERT, J. R.; YOUNGS, W. J. *J. Am. Chem. Soc.* **1980**, 102, 4515.
- 46 (a) KRESS, J.; WESOLEK, M.; OSBORN, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 514. (b) KRESS, J.; OSBORN, J. A. *J. Am. Chem. Soc.* **1983**, 105, 6346.
- 47 (a) IVIN, K. J.; LAVERTY, D. T.; ROONEY, J. J. *Makromol. Chem.* **1977**, 178, 1545. (b) IVIN, K. J.; LAVERTY, D. T.; ROONEY, J. J. *Rec. Trav. Chim. Pays-Bas* **1977**, 96, M54. (c) IVIN, K. J.; LAPIENIS, G.; ROONEY, J. J. *J. Chem. Soc., Chem. Commun.* **1979**, 1068. (d) IVIN, K. J.; LAPIENIS, G.; ROONEY, J. J. *Polymer* **1980**, 21, 436. (e) HO, H. T.; IVIN, K. J.; ROONEY, J. J. *Makromol. Chem.* **1982**, 183, 1629.
- 48 (a) FEAST, W. J.; WILSON, B. *Polymer* **1979**, 20, 1182. (b) FEAST, W. J.; WILSON, B. *J. Mol. Catal.* **1980**, 8, 277. (c) BLACKMORE, P. M.; FEAST, W. J. *Polymer* **1986**, 27, 1296.
- 49 (a) HOWARD, T. R.; LEE, J. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1980**, 102, 6878. (b) LEE, J. B.; OTT, K. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1982**, 104, 7491.
- 50 RUPPRECHT, G. A.; MESSERLY, L. W.; FELLMANN, J. D.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1980**, 102, 6236.
- 51 McLAIN, S. J.; WOOD, C. D.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1977**, 99, 3519.
- 52 (a) OFSTEAD, E. A.; CALDERON, N. *Makromol. Chem.* **1972**, 154, 21. (b) HÖCKER, H.; MÜSCH, R. *Makromol. Chem.* **1972**, 157, 201.
- 53 (a) GILLIOM, L. R.; GRUBBS, R. H. *Organometallics* **1986**, 5, 721. (b) GILLIOM, L. R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1986**, 108, 733. (c) GRUBBS, R. H.; GILLIOM, L. R. *Proceedings of the 4th International Symposium on Homogeneous Catalysis*, 24–28 September 1984, Leningrad, USSR.
- 54 (a) PINE, S. H.; ZAHLER, R.; EVANS, D. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1980**, 102, 3270. (b) BROWN-WENSLEY, K. A.; BUCHWALD, S. L.; CANNIZZO, L.; CLAWSON, L.; HO, S.; MEINHARDT, D.; STILLE, J. R.; GRUBBS, R. H. *Pure Appl. Chem.* **1983**, 55, 1733.
- 55 CANNIZZO, L. F.; GRUBBS, R. H. *Macromolecules* **1988**, 21, 1961.
- 56 RISSE, W.; GRUBBS, R. H. *Macromolecules* **1989**, 22, 4462.
- 57 RISSE, W.; GRUBBS, R. H. *Macromolecules* **1989**, 22, 1558.
- 58 RISSE, W.; WHEELER, D. R.; CANNIZZO, L. F.; GRUBBS, R. H. *Macromolecules* **1989**, 32, 3205.
- 59 (a) WALLACE, K. C.; DEWAN, J. C.; SCHROCK, R. R. *Organometallics* **1986**, 5, 2162. (b) WALLACE, K. C.; SCHROCK, R. R. *Macromolecules* **1987**, 20, 450. (c) WALLACE, K. C.; LIU, A. H.; DEWAN, J. C.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1988**, 110, 4964.
- 60 QUIGNARD, F.; LECONTE, M.; BASSET, J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1816.
- 61 (a) KRESS, J.; OSBORN, J. A.; GREENE, R. M. E.; IVIN, K. J.; ROONEY, J. J. *J. Am. Chem. Soc.* **1987**, 109, 899. (b) KRESS, J.; OSBORN, J. A.; AMIR-EBRAHIMI, V.; IVIN, K. J.; ROONEY, J. J. *J. Chem. Soc.* **1988**, 1164. (c) KRESS, J.; OSBORN, J. A.; IVIN, K. J. *J. Chem. Soc.* **1989**, 1234. (d) KRESS, J.; IVIN, K. J.; AMIR-EBRAHIMI, V.; WEBER, P. *Makromol. Chem.* **1990**, 191, 2237.
- 62 IVIN, K. J.; KRESS, J.; OSBORN, J. A. *J. Mol. Catal.* **1988**, 46, 351.
- 63 HEPPERT, J. A.; DIETZ, S. D.; EILERTS, N. W.; HENNING, R. W.; MORTON, M. D.; TAKUSAGAWA, F.; KAUL, F. A. *Organometallics* **1993**, 12, 2565.
- 64 FELDMAN, J.; SCHROCK, R. R. *Prog. Inorg. Chem.* **1991**, 39, 1.
- 65 (a) SCHAUVERIEN, C. J.; DEWAN, J. C.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1986**, 108, 2771. (b) SCHROCK, R. R.; DEPUÉ, R. T.; FELDMAN, J.; SCHAUVERIEN, C. J.; DEWAN, J. C.; LIU, A. H. *J. Am. Chem. Soc.* **1988**, 110, 1423.
- 66 (a) MURDZEK, J. S.; SCHROCK, R. R. *Macromolecules* **1987**, 20, 2640. (b) SCHROCK, R. R.; MURDZEK, J. S.;

- BAZAN, G. C.; ROBBINS, J.; DIMARE, M.; O'REGAN, M. J. *Am. Chem. Soc.* **1990**, *112*, 3875.
- 67 SCHROCK, R. R.; FELDMAN, J.; CANNIZZO, L. F.; GRUBBS, R. H. *Macromolecules* **1987**, *20*, 1169.
- 68 O'DONOGHUE, M. B.; SCHROCK, R. R.; LAPOINTE, A. M.; DAVIS, W. M. *Organometallics* **1996**, *15*, 1334.
- 69 BAZAN, G. C.; SCHROCK, R. R.; CHO, H.-N.; GIBSON, V. C. *Macromolecules* **1991**, *24*, 4495.
- 70 (a) GOLD, L. J. *Chem. Phys.* **1958**, *28*, 91. (b) REMPP, P.; MERRILL, E. W. *Polymer Synthesis*, Huethig and Wepf, New York, 1986.
- 71 (a) BAZAN, G. C.; SCHROCK, R. R. *Macromolecules* **1990**, *24*, 817. (b) BAZAN, G. C.; KHOSRAVI, E.; SCHROCK, R. R.; FEAST, W. J.; GIBSON, V. C.; O'REGAN, M. B.; THOMAS, J. K.; DAVIS, W. M. J. *Am. Chem. Soc.* **1990**, *112*, 8378.
- 72 BAZAN, G. C.; OSKAM, J. H.; CHO, H.-N.; PARK, L. Y.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.
- 73 (a) COLES, M. P.; GIBSON, V. C.; MAZZARIOL, L.; NORTH, M.; TEASDALE, W. G.; WILLIAMS, C. M.; ZAMUNER, D. J. *Chem. Soc., Chem. Commun.* **1994**, 2505. (b) BIAGINI, S. C. G.; COLES, M. P.; GIBSON, V. C.; GILES, M. R.; MARSHALL, E. L.; NORTH, M. *Polymer* **1998**, *39*, 1007.
- 74 (a) KHOSRAVI, E.; AL-HAJAJI, A. A. *Polymer* **1998**, *39*, 5619. (b) KHOSRAVI, E.; FEAST, W. J.; AL-HAJAJI, A. A.; LEEJARKPAI, T. J. *Mol. Catal. A: Chem.* **2000**, *160*, 1.
- 75 (a) FEAST, W. J.; GIBSON, V. C.; MARSHALL, E. L. *J. Chem. Soc., Chem. Commun.* **1992**, 1157. (b) MCCONVILLE, D. H.; WOLF, J. R.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 4413.
- 76 O'DELL, R.; MCCONVILLE, D. H.; HOFMEISTER, G. E.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 3414.
- 77 OSKAM, J. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11831.
- 78 SCHROCK, R. R.; LEE, J.-K.; O'DELL, R.; OSKAM, J. H. *Macromolecules* **1995**, *28*, 5933.
- 79 TOTLAND, K. M.; BOYD, T. J.; LAVOIE, G. G.; DAVIS, W. M.; SCHROCK, R. R. *Macromolecules* **1996**, *29*, 6114.
- 80 FOX, H. H.; LEE, J.-K.; PARK, L. Y.; SCHROCK, R. R. *Organometallics* **1993**, *12*, 759.
- 81 WU, Z.; WHEELER, D. R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 146.
- 82 WU, Z.; GRUBBS, R. H. *Macromolecules* **1994**, *27*, 6700.
- 83 (a) EDWARDS, J. H.; FEAST, W. J.; BOTT, D. C. *Polymer* **1984**, *25*, 395. (b) LEISING, G. *Polymer Bull.* **1984**, *11*, 401.
- 84 (a) KNOLL, K.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1989**, *111*, 7989. (b) PARK, L. Y.; SCHROCK, R. R.; STIEGLITZ, S. G.; CROWE, W. E. *Macromolecules* **1991**, *24*, 3489.
- 85 CONTICELLO, V. P.; GIN, D. L.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 9708.
- 86 WAGAMAN, M. W.; GRUBBS, R. H. *Macromolecules* **1997**, *30*, 3978.
- 87 (a) WU, Z.; GRUBBS, R. H. *Macromolecules* **1995**, *28*, 3502. (b) ALDER, R. W.; ALLEN, P. R.; KHOSRAVI, E. *J. Chem. Soc., Chem. Commun.* **1994**, 1235.
- 88 (a) PERROTT, M. G.; NOVAK, B. M. *Macromolecules* **1995**, *28*, 3492. (b) PERROTT, M. G.; NOVAK, B. M. *Macromolecules* **1996**, *29*, 1817.
- 89 (a) SCHROCK, R. R.; KROUSE, S. A.; KNOLL, K.; FELDMAN, J.; MURDZEK, J. S.; YANG, D. C. *J. Mol. Catal.* **1988**, *46*, 243. (b) SCHROCK, R. R.; YAP, K. B.; YANG, D. C.; SITZMANN, H.; SITA, L. R.; BAZAN, G. C. *Macromolecules* **1989**, *22*, 3191.
- 90 (a) DOUNIS, P.; FEAST, W. J. *Polymer* **1996**, *37*, 2547. (b) TRZASKA, S. T.; LEE, L.-B. W.; REGISTER, R. A. *Macromolecules* **2000**, *33*, 9215.
- 91 (a) MIAO, Y.-J.; BAZAN, G. C. *J. Am. Chem. Soc.* **1994**, *116*, 9379. (b) MIAO, Y.-J.; BAZAN, G. C. *Macromolecules* **1994**, *27*, 1063. (c) BAZAN, G. C.; MIAO, Y.-J.; RENAK, M. L.; SUN, B. J. *J. Am. Chem. Soc.* **1996**, *118*, 2618.
- 92 (a) NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) NGUYEN, S. T.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858.

- 93 SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
- 94 KANOAKA, S.; GRUBBS, R. H. *Macromolecules* **1995**, *28*, 4707.
- 95 SCHWAB, P.; FRANCE, M. B.; ZILLER, J. W.; GRUBBS, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.
- 96 ROBSON, D. A.; GIBSON, V. C.; DAVIES, R. G.; NORTH, M. *Macromolecules* **1999**, *32*, 6371.
- 97 SANFORD, M. S.; LOVE, J. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
- 98 BIELAWSKI, C. W.; GRUBBS, R. H. *Macromolecules* **2001**, *34*, 8838.
- 99 (a) WU, Z.; BENEDICTO, A. D.; GRUBBS, R. H. *Macromolecules* **1993**, *26*, 4975. (b) WU, Z. *Ph.D Thesis*, The California Institute of Technology, 1994.
- 100 MAUGHON, B. R.; GRUBBS, R. H. *Macromolecules* **1997**, *30*, 3459.
- 101 CHARVET, R.; NOVAK, B. M. *Macromolecules* **2001**, *34*, 7680.
- 102 RISSE, W.; DESTRO, M. *Abstracts of Papers of the American Chemical Society*, 224, 306-Orgn, Part 2, Boston, August 2002.
- 103 HILLMYER, M. A.; LAREDO, W. R.; GRUBBS, R. H. *Macromolecules* **1995**, *28*, 6311.
- 104 MECKING, S.; HELD, A.; BAUERS, F. M. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 545.
- 105 (a) LYNN, D. M.; KANOAKA, S.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 784-790.
- 106 (a) LYNN, D. M.; MOHR, B.; GRUBBS, R. H.; HENLING, L. M.; DAY, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601. (b) LYNN, D. M.; MOHR, B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627.
- 107 CLAVERIE, J. P.; VIALA, S.; MAUREL, V.; NOVAT, C. *Macromolecules* **2001**, *34*, 382.
- 108 (a) CAIRO, C. W.; GESTWICKI, J. E.; KANAI, M.; KIESSLING, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 1615. (b) MANNING, D. D.; HU, X.; BECK, P.; KIESSLING, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 3161.
- 109 (a) LINDHORST, T. K. *Top. Curr. Chem.* **2002**, *218*, 201. (b) OKADA, M. *Prog. Polym. Sci.* **2001**, *26*, 67. (c) GORDON, E. J.; GESTWICKI, J. E.; STRONG, L. E.; KIESSLING, L. L. *Chem. Biol.* **2000**, *7*, 9. (d) FRASER, C.; GRUBBS, R. H. *Macromolecules* **1995**, *28*, 7248. (e) NOMURA, K.; SCHROCK, R. R. *Macromolecules* **1996**, *29*, 540.
- 110 MOHR, B.; LYNN, D. M.; GRUBBS, R. H. *Organometallics* **1996**, *15*, 4317.
- 111 WU, Z.; NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503.
- 112 WECK, M.; SCHWAB, P.; GRUBBS, R. H. *Macromolecules* **1996**, *19*, 1789.
- 113 DIAS, E. L.; GRUBBS, R. H. *Organo-metallics* **1998**, *17*, 2758.
- 114 (a) CHATTERJEE, A. K.; MORGAN, J. P.; SCHOLL, M.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953. (c) HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSON, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (d) WESKAMP, T.; KOHL, F. J.; HIERINGER, W.; GLEICH, D.; HERRMANN, W. A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2416. (e) HERRMANN, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1291.
- 115 BIELAWSKI, C. W.; GRUBBS, R. H. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2903.
- 116 FRENZEL, U.; WESKAMP, T.; KOHL, F. J.; SCHATTENMANN, W. C.; NUYKEN, O.; HERRMANN, W. A. *J. Organomet. Chem.* **1999**, *586*, 263.
- 117 BIELAWSKI, C. W.; BENITEZ, D.; MORITA, T.; GRUBBS, R. H. *Macromolecules* **2001**, *34*, 8610.
- 118 (a) MAYNARD, H. D.; OKADA, S. Y.; GRUBBS, R. H. *Macromolecules* **2000**, *33*, 6239. (b) MAYNARD, H. D.; OKADA, S. Y.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 1275.
- 119 (a) BAZAN, G. C.; SCHROCK, R. R. *Macromolecules* **1991**, *24*, 817. (b) SAUNDERS, R. S.; COHEN, R. E.; WONG, S. J.; SCHROCK, R. R. *Macromolecules* **1992**, *25*, 2055. (c) CONNOR, E. F.; LARES, M. C.; HEDRICK, J. L.; MILLER, R. D. *Polymer Preprints* **2002**, *43*(1), 724.
- 120 WORSFOLD, D. J.; ZILLIOX, J. G.; REMPP, P. *Can. J. Chem.* **1969**, *47*, 3379.

3.3

Synthesis of Copolymers

Ezat Khosravi

3.3.1

Introduction

Control over macromolecular architecture and resulting material properties has been a central goal of polymer chemistry. There has been much interest in developing new synthetic routes to prepare copolymers with novel compositions and topologies. Efforts have been directed toward developing new synthetic methodologies whereby precise placement of chemical functionality and monomer composition can be achieved. Copolymerization is a very important process that allows, in many cases, the alteration of the physical, mechanical, and electronic properties of a material through adjustments to the ratio of copolymer's individual components. Ring-opening metathesis polymerization (ROMP) has attracted considerable research attention recently largely due to development of well-defined initiator systems. ROMP using well-defined initiators is a living process and therefore allows the synthesis of well-defined polymers with controlled architectures, molecular weights, polydispersities, and terminal functionalities. This chapter aims at reviewing the synthetic routes developed recently for preparing novel copolymers based on ROMP and its combination with other polymerization techniques. It highlights the impact of the well-defined ROMP initiators and the utility of ROMP as a powerful technique for the synthesis of new materials with well-defined structures.

3.3.2

Random Copolymers

Random copolymers are prepared by ROMP of a mixture of monomers. In this type of polymerization, the reactivity of the monomers plays a very important role, particularly in the composition of each monomer in the final copolymer product. Some apparent reactivity ratios for various pairs of monomers have been summarized [1]. Broadly speaking, reactivities of monomers towards a given propagating species lie in the order: cyclobutene derivatives > norbornene and its 5-substituted derivatives > cyclopentene and larger rings.

In a living system, if M_1 is much more reactive than M_2 and polymerization is allowed to proceed to completion, the end product is a tapered block copolymer, in which only the middle section contain units of both monomers, e.g., with *anti*-7-methylnorbornene (M_1)/*syn*-7-methylnorbornene (M_2), catalyzed by a tungsten-cyclopentylidene complex [2], or norbornene (M_1)/cyclooctatetraene (M_2), catalyzed by $W(=CHCMe_3)(=NAr)[OCMe(CF_3)_2]_2$ [3]. In the extreme case, the cross-propagation reactions may be so slight that the product is indistinguishable from a perfect block copolymer, e.g., with bicyclo[3.2.0]hept-2-ene (M_1)/norbornene (M_2), catalyzed by $Ru(=CHCH=CPh_2)(Cl)_2(PPh_3)_2$ [4, 5], or with *anti*-7-methylnorbornene (M_1)/*syn*-7-methylnorbornene (M_2), catalyzed by $Mo(=CHMe_3)(=NAr)(OCMe_3)_2$ [6]. The successive polymerization of the two monomers can be readily followed by 1H NMR.

For 5-substituted norbornenes, the *exo*-isomer is usually rather more reactive than the *endo*-isomer. An extreme case is provided by the *exo*- and *endo*-isomers obtained by the Diels-Alder reaction of cyclopentadiene and maleic anhydride. The aforementioned tungsten-cyclopentylidene complex at first brings about the selective ROMP of the *exo*-isomer, but when this is all consumed, the carbene proton signal corresponding to the addition of the *endo*-isomer begins to appear and this isomer then slowly adds to the chain [7].

The fullerene monomer (Figure 3.3-1) can be copolymerized with an excess of norbornene in the presence of $Mo(=CHCMe_3)(=NAr)[OCMe(CF_3)_2]_2$ to yield a high-molecular-weight, soluble, film-forming copolymer (86% *cis*) containing 1% of C60 derivative and exhibiting electronic and electrochemical properties that are typical of the carbon cluster [8].

Copolymerization of the benzocrown ether and benzocrown ether with pendant phenylalanine methyl esters and phenylalanine carboxylic acids (Scheme 3.3-1) using $Ru(=CHPh)(Cl)_2(PCy_3)_2$ produced random polyether copolymers [9]. The copolymer composition corresponded to the feed ratio of the monomers. In addi-

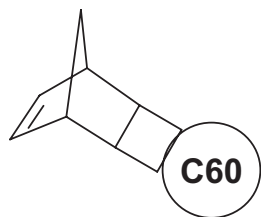
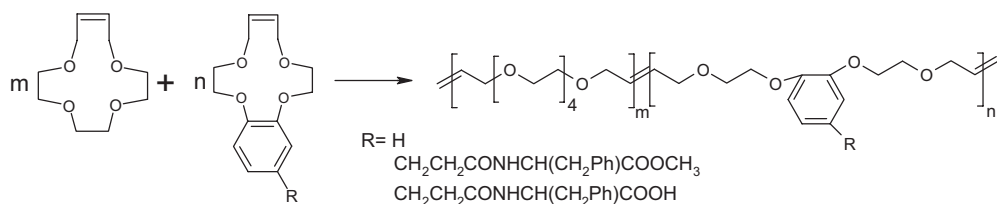


Fig. 3.3-1. Fullerene norbornene monomer.



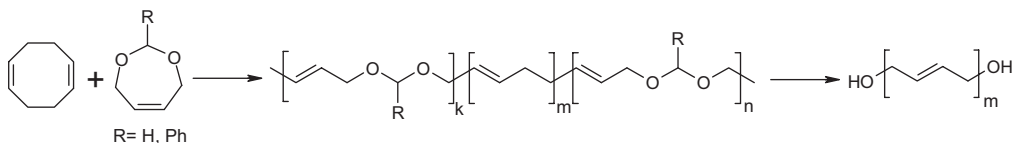
Scheme 3.3-1

tion to synthesizing polyethers with new backbone structures, the synthesis of these polymers with pendant amino acids demonstrated the feasibility of producing biorelevant polyethers via ROMP. An advantage of synthesizing materials in this way is the ability to produce polymers with many bioactive groups per polymer chain where the number of groups can be readily controlled by the initial concentrations of the monomers. Such polymers have potential uses in tissue engineering, drug delivery, and other biomedical applications.

Polymers that can be cleaved at specific sites along the chains are of interest as precursors to telechelic polymers [10]. These polymers bearing functionalities at both termini are useful as macromonomers in condensation polymerization and as precursors for the preparation of block copolymers, and they have been exploited in network formation, among other applications [11]. Hydroxytelechelic polybutadiene (HTPBD), for example, has been used in polyurethane synthesis to impart elastomeric and other desirable properties [12–14]. HTPBD has been prepared by metathesis degradation [15] and ROMP of COD in the presence of chain-transfer reagents [16]. Commercial HTPBD, prepared via the radical method, results in mixtures of 1,2 and 1,4 repeat units and at least three different types of hydroxyl end groups [17, 18]. A different route has been described to prepare 1,4-HTPBD, involving selective decomposition of degradable copolymers prepared by ROMP. 1,4-Hydroxytelechelic polybutadiene (HTPBD) was obtained upon fragmentation of a copolymer of COD and 4,7-dihydroxy-2-phenyl-1,3-dioxepin (Scheme 3.3-2) at the benzylidene acetal functionalities by stirring with acids (aqueous HCl/MeOH, aqueous H₂SO₄, or trifluoroacetic acid/MeOH in CH₂Cl₂). Polydispersities for 1,4-HTPBD prepared from COD/benzylidene acetal copolymer were ~1.1–1.3 when using (PCy₃)₂Cl₂Ru=CHCH=CPh₂ and (PCy₃)₂Cl₂Ru=CHPh as initiators [19].

The COD/acetal copolymers are also of interest since they allow entry into derivatives of polyethylene. For example, selective hydrogenation of the olefins of acetal-containing copolymers would result in a degradable polyethylene, that is, polyethylene with acetal moieties distributed along the backbone [19]. COD/benzylidene acetal copolymer was simultaneously hydrogenated and degraded in one step using *p*-toluenesulfonohydrazide to produce hydroxytelechelic polyethylene.

Many extracellular matrix proteins bind to cell surface through the short peptide sequence Arg-Gly-Asp (RGD) [20]. Since cell attachment mediated by integrin-protein interactions influences cell survival, differentiation, and migration, this sequence has been targeted to study integrin function and provide treatments for



Scheme 3.3-2

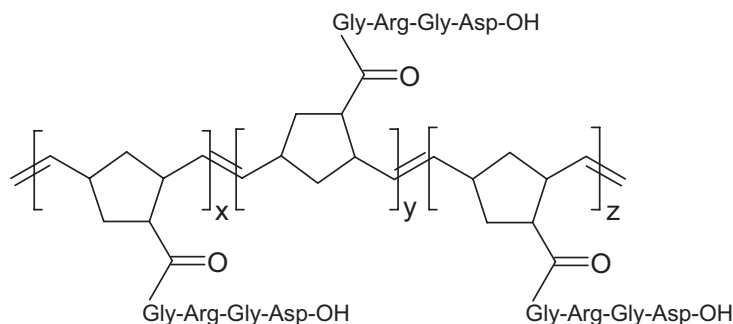
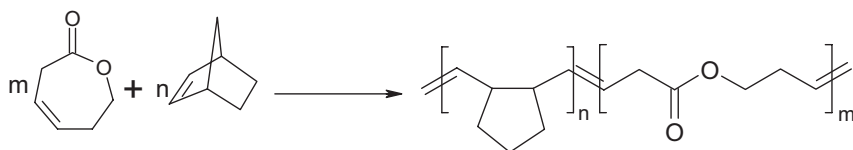


Fig. 3.3-2. Target polymer containing GRGD, SRN and EO5 pendant groups.

diseases [21]. Synthetic polymers containing pendant RDGs should be very useful in these applications, especially since multiple RGDs could lead to multivalent interactions and stronger binding [22]. A synthetic polymer with RGD units linked to a poly(carboxyethylmethacrylamide) backbone has been reported and was shown to have increased therapeutic potential to cancer metastasis compared with the free peptide [23]. However, this polymer was synthesized by nonliving, radical polymerization, which provides little control over molecular weight and resulted in PDIs between 2 and 2.4.

The synthesis of norbornenyl polymers with the pendant cell-adhesive sequences glycine-arginine-glycine-aspartic (GRGD) and serin-arginine-asparagine (SRN) of the type shown in Figure 3.3-2 has been reported [24]. Norbornene monomers with pendant glycine-arginine-glycine-aspartic (GRGD) and serin-arginine-asparagine (SRN) were synthesized and copolymerized with norbornene monomer with pendant penta(ethylene oxide) (EO5) by ROMP using ruthenium initiators $(\text{PCp}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ (1), $(\text{PCy}_3)(\text{DHIMes})\text{Cl}_2\text{Ru}=\text{CHPh}$ (2), and $(\text{PCy}_3)(\text{DHIMes})\text{Cl}_2\text{Ru}=\text{CHCH}=\text{C}(\text{CH}_3)_2$ (3). Copolymers containing 9.2 mol% GRGD were synthesized using initiator 1. However, incorporating larger amounts of GRGD resulted in extremely low yields of polymers that exhibited bimodal molecular weight distributions. Copolymers with larger amounts of GRGD and SRN were synthesized in good yields (32–92%), with monomodal molecular weight distributions, using initiators 2 and 3. In this way, EO5 containing copolymers with 49 mol% GRDG, 53 mol% SRN, or 32 mol% GRGD and 21 mol% SRN were synthesized. The polymers containing GRGD and SRN have potential applications in a variety of fundamental research studies of the binding of integrins to proteins and for many disease-related applications such as tumor therapy.

6,7-Dihydro-2(3H)-oxepinone (DHO2) is an interesting unsaturated ϵ -caprolactone monomer because it is polymerizable by ring-opening polymerization and ROMP. This monomer has been copolymerized with NBE, *cis*-cyclooctene, and COD by using Schrock's molybdenumhexafluoroneophylidene(dimethylimido) (Scheme 3.3-3) [25]. The initiator was added to the mixtures of DHO2/cyclic olefins in toluene at 60 °C for 17 h. Generally, yields were about 70–75%, PDIs were broad (1.8–5.3), and the copolymer contained fewer DHO2 units than the comono-



Scheme 3.3-3

monomer feed, which indicated a lower reactivity for DHO2 compared to the cyclic olefins.

3.3.3

Block Copolymers

3.3.3.1

Sequential Addition of Monomers

The most convenient way to prepare a block copolymer of the A-B or A-B-A type is the sequential addition of monomers to a living polymerization system [26–28]. Living or controlled/living polymerization techniques allow the synthesis of well-defined polymers with controlled molecular weight, polydispersities, and terminal functionalities. In these systems the contribution of termination reactions is absent or insignificant, the polymerization proceeds until all of the monomer has been consumed, and further addition of monomer results in continued polymerization. Living or controlled/living polymerization can proceed by anionic [29], cationic [30, 31], group transfer [32], Zeigler-Natta [33–35], or radical mechanisms [36–40].

The early ill-defined classical ROMP initiator systems were unsuited to the preparation of block copolymers, and the great advance in this area came with the development of the well-defined ROMP initiators. The first indications that these would provide a practical method of making long-chain block copolymers came with the observation that the propagating tungsten-carbene species P_1 derived from monomer M_1 (norbornene) could be readily converted, by adding a second monomer M_2 (endo-5-methylnorbornene), to the propagating species P_2 and then back again to P_1 by a further addition of M_1 [41]. This was followed by qualitative observations of the appropriate increase in MW after each addition of monomer [42] and by more quantitative studies that showed that block copolymers could be made with a narrow MWD ($M_w/M_n < 1.1$), even from norbornene derivatives containing ester groups [43]. Most of the early examples of block copolymers consisted of non-polar segments because of the difficulty in preparing living polymers with polar functional groups by early transition metal catalysts. It was not until recently that block copolymers with pendant polar functional groups have been synthesized using well-defined initiators that are tolerant of a variety of functional groups.

In the formation of block copolymers by sequential addition of monomers, it generally does not matter which monomer is polymerized first, and diblock or

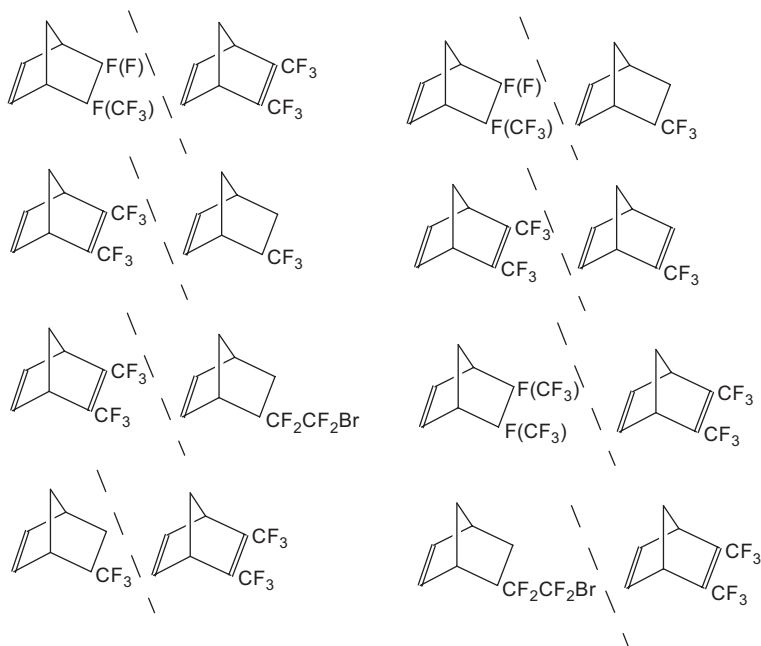


Fig. 3.3-3. Selection of fluorinated norbornene monomer pairs giving rise to successful block copolymer synthesis, the monomer on the left was polymerised first.

multi-block copolymers of narrow MWD and of any desired sequence length are readily prepared. Occasionally, one may be troubled by slow initiation relative to propagation at the second stage, leading to a broadened MWD, but such difficulties can usually be overcome by careful attention to ligands. Secondary metathesis reactions of the copolymer can also broaden the MWD. If the two component monomers are of similar polarity there is no observable phase separation within the block copolymer, and DSC shows a single glass transition temperature T_g . When there is a larger difference in polarity, microphase separation can generally be detected by one or more of a variety of techniques.

Fluorinated block copolymers from a range of fluorinated norbornenes and norbornadienes, illustrated in Figure 3.3-3, have been produced using Schrock's well-defined molybdenum initiator in a living manner by the sequential addition of monomers [44]. The advantage of these systems, illustrated in Figure 3.3-3, is that the complete course of the copolymerization reactions can be followed by ^1H NMR. When the first monomer is polymerized, characteristic propagating alkylidene resonances are seen in the ^1H NMR spectrum. When the comonomer is added, after the complete polymerization of the first monomer, a new propagating alkylidene signal typical of the second monomer appears.

GPC analysis of the block copolymer samples revealed that the samples exhibit narrow molecular weight distributions. Some of the fluorinated block copolymers

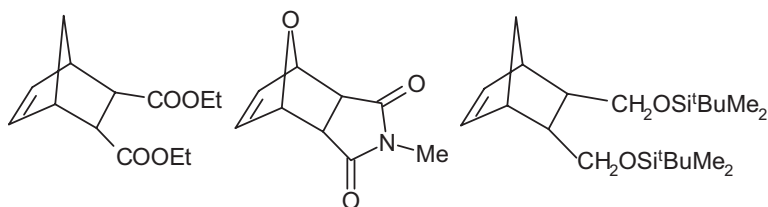
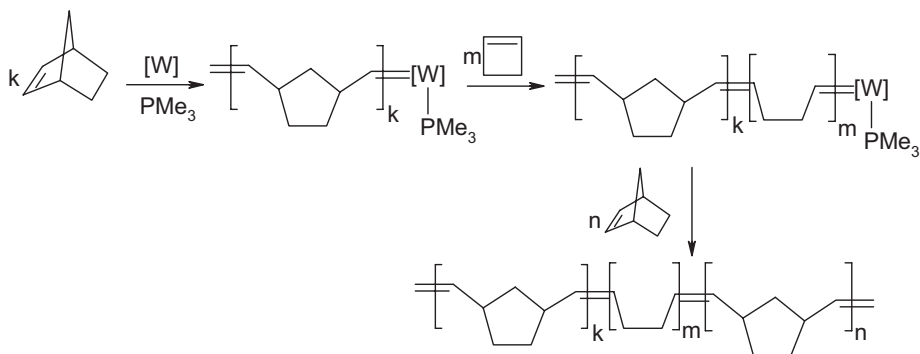


Fig. 3.3-4. Monomers used for the synthesis of silicon-containing block copolymers.

show two glass transition temperatures that are well defined; this observation has been confirmed by thermally stimulated current (TSC) studies. This provides clear evidence that the two components are not compatible.

Silicon-containing homopolymers, block copolymers, and end-functionalized polymers have interesting properties such as gas permeability and also offer potential as semiconductors, photoconductors, and nonlinear optical materials [45]. Silicon-containing block copolymers with narrow molecular weight distribution have been prepared by sequentially polymerizing norbornene derivative and 7-oxanorbornene derivative with silicon-containing norbornene derivative (Figure 3.3-4) using the ruthenium initiators $(\text{PPh}_3)_2\text{Cl}_2\text{Ru}=\text{CHCH}=\text{CPh}_2$ and $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHCH}=\text{CPh}_2$ [46].

Polyethylene is an important commercial material, and monodispersed linear polyethylene has long been both a synthetic challenge and of theoretical interest [47]. Low polydispersity polyethylene has been synthesized by hydrogenation of 1,4-polybutadiene prepared by anionic polymerization of 1,3-butadiene. This approach results in branched polyethylene, since polybutadiene produced by this technique contains C_2 branches as a result of the low level of 1,2-polymerization of 1,3-butadiene [47]. A living polymerization system has been developed for the ROMP of cyclobutane that is based on Schrock's tungsten-neopentylidene initiator and addition of 5–10 equivalents of PMe_3 [48, 49]. This polymerization system produced the first linear near monodisperse ($\text{PDI} < 1.1$) polyethylene. The same polymerization system was used to prepare norbornene-cyclobutene diblock and norbornene-cyclobutene-norbornene triblock copolymers (Scheme 3.3-4) with



Scheme 3.3-4

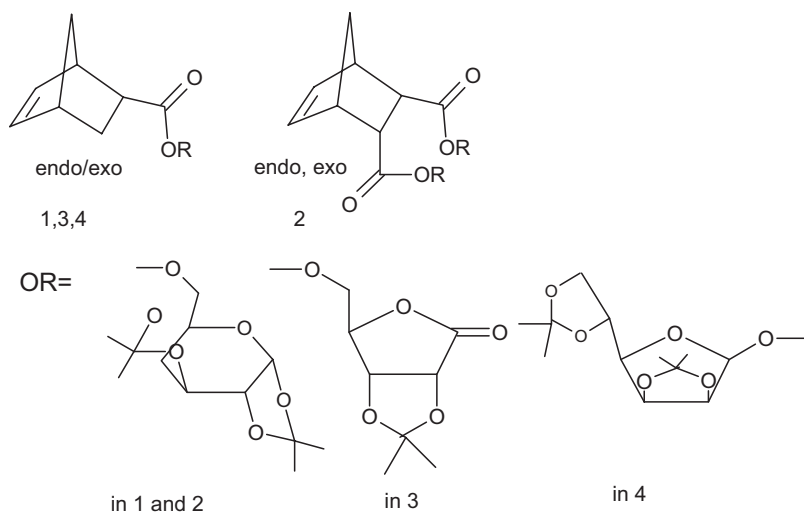
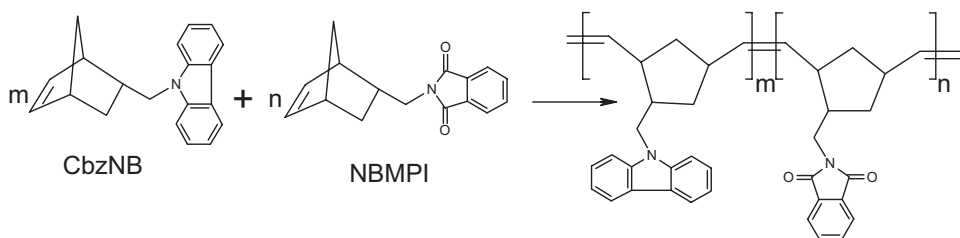


Fig. 3.3-5. Norbornene mono- and di-carboxylates containing acetal-protected sugars.

a polydispersity of 1.05–1.08 [49]. The hydrogenation of these copolymers gave poly(hydrogenated norbornene-PE) and poly(hydrogenated norbornene-PE-hydrogenated norbornene).

One of the potential applications of ROMP by well-defined initiators such as $\text{Mo}(\text{CHCMe}_2\text{Ph})(\text{NAr})(\text{O}-t\text{-Bu})_2$ is the synthesis of hydrophilic or water-soluble polymers by using a monomer that contains a protected functionality. Carbohydrate-based polymers, especially well-controlled, low polydispersity homopolymers and block copolymers that contain identified end groups, could be particularly interesting, not only from the viewpoint of solubility in water [50]. For example, polymers that have an unnatural or abiological backbone but natural sugars as side groups could have applications in biology, e.g., cell surface recognition [51] or protein stabilization [52]. The synthesis of sugar-coated polymers by ROMP using molybdenum initiator has been reported. Di-, tri, and tetrablock copolymers containing monomers 1–4 and methyltetracyclododecene (MTD) or trans-2,3-bis((trimethylsilyl)oxy)methyl-norborn-5-ene (Figure 3.3-5) were prepared and were found to have low polydispersity ($\text{PDI} = 1.03\text{--}1.25$) [53]. The cyclic acetal in polymers containing monomers 1 or 2 could be removed using $\text{CF}_3\text{COOH}/\text{H}_2\text{O}$ (9/1 v/v, 15 min., 22 °C) to afford the corresponding water-soluble polymers containing the parent sugar.

Carbazoyl-substituted polymers are well known as precursors for electrophotographical materials with valuable optical, photoconductive, and other useful applications such as organic light-emitting diodes [54]. The polymers bearing phthalimide group as a pendant group exhibit high thermal stability and good solubility [55, 56]. Block copolymers of 5-(*N*-carbazoyl methyl)bicycle[2.2.1]hept-2-ene (CbzNB) and 5-(phthalimide methyl)bicycle[2.2.1]hept-2-ene (NBMPI) (Scheme 3.3-5) have been synthesized via ROMP using $\text{RuCl}_2(\text{CHPh})(\text{PCy}_3)_2$ [57]. The



Scheme 3.3-5

block copolymers produced exhibited M_n in the range 98,000–610,000 and PDI in the range 1.35–1.54. The block copolymers were hydrogenated using *p*-toluenesulfonylhydrazide as reducing agent. Hydrogenated and unhydrogenated diblock copolymers exhibited strong carbazole fluorescence. All diblock copolymers exhibited good solubility. Two T_g values were observed for the CbzNB and NBMPI segments before and after hydrogenation. They all showed good thermal stability, losing 10% mass at 380 °C. Furthermore, the diblock copolymer of 5-(*N*-methylbicyclo[2.2.1]hept-2-ene (CbzNB) with COD has also been synthesized by ROMP using $\text{RuCl}_2(\text{CHPh})(\text{PCy}_3)_2$ [58]. The block copolymer produced exhibited M_n of 140,000–255,000 and PDI of 1.1–1.47. Diblock copolymers exhibited strong carbazole fluorescence, with monomer emission in the near-UV at approximately 377 nm and extending into the blue-violet region. The block copolymers were hydrogenated using *p*-toluenesulfonylhydrazide as reducing agent. Diblock copolymers should have two T_g values due to the poly(CbzNB) and poly(butadiene) segments. However, after hydrogenation, they showed only one T_g for the poly(CbzNB) segment and one T_m for the polyethylene segment. The diblock copolymers with the longer CbzNB segment exhibited better thermal stability than the copolymers with the shorter segments of CbzNB.

In recent years considerable effort has been directed to the synthesis of novel side-chain liquid crystalline polymers because of a variety of applications, especially in the field of electrooptics [59, 60]. Side-chain liquid crystallinity generally requires a molecular structure in which a flexible polymer chain, or flexible connector group between the mesogen and backbone, provides sufficient conformational freedom to allow the rigid mesogenic units to form stacks or organized domains [61, 62]. Side-chain liquid crystalline polymers (SCLCPs) have been prepared mainly by radical polymerization of mesogenic acrylates and methacrylates. Because it is difficult to control both the molecular weight and the polydispersity of the resulting polymers, it is of limited use for determining the influence of molecular weight distribution on the phase behavior of SCLCPs [63]. More recent advances have witnessed the use of living ROMP in the synthesis of SCLCPs [64–70]. Schrock and coworkers have reported the living ROMP of mesogenic norbornene derivatives using $\text{Mo}(\text{CH-t-Bu})(\text{NAr})(\text{O-t-Bu})_2$ as the initiator [64, 68]. Diblock copolymers having well-defined block lengths often produce microphase-separated morphologies (lamellae, cylinders, or spheres) in cast films. If one of the blocks were a SCLCP, then one would expect a liquid crystalline (LC) microphase to form within one of the microdomains. This has been demonstrated in the syn-

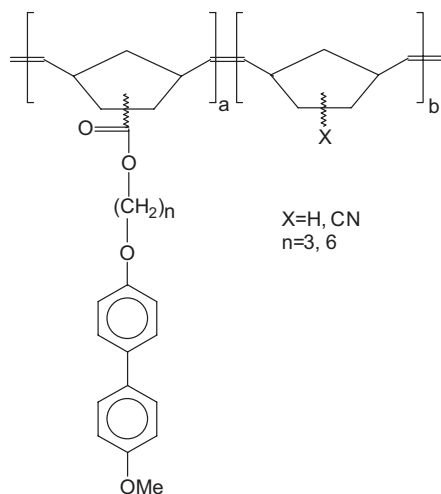
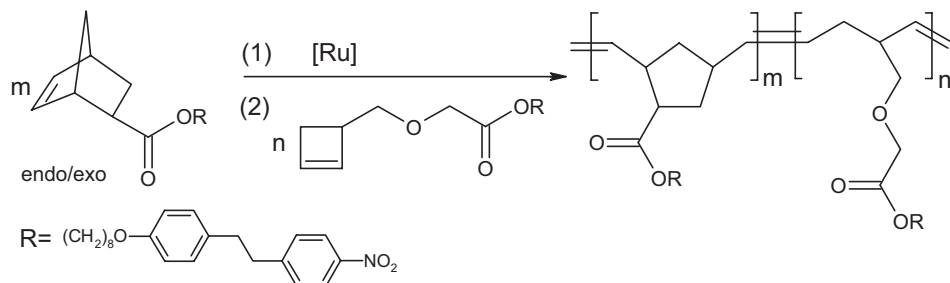


Fig. 3.3-6. Block copolymer containing a SCLCP block and an amorphous block.

thesis of AB-type block copolymers that contain a SCLCP block and an amorphous polymer block by employing living ROMP. Norbornene, 5-cyano-2-norbornene, and methyltetracyclododecene were used for the amorphous polymer blocks, and n -[(((4'-methoxy-4-biphenyl)yl)oxy]alkyl bicyclo [2.2.1]hept-2-ene-5-carboxylates (Figure 3.3-6) were used for the SCLCP block [67].

The effect of backbone flexibility on the mesomorphic behavior of side-chain liquid crystalline polymers synthesized by ROMP has been investigated [71, 72]. The relatively rigid poly(norbornene)s displayed enantiotropic, nematic mesomorphism with glass transitions from 44 °C to 64 °C and isotropization temperatures between 108 °C and 121 °C, whereas the more flexible poly(butadiene)s produced by ROMP of cyclobutanes showed enantiotropic smectic A mesomorphism with glass transition temperatures from 14 °C to 31 °C and isotropization temperatures between 74 °C and 111 °C. Surprisingly, a diblock copolymer containing a 1:1 mixture of the poly(norbornene) and poly(butadiene) (Scheme 3.3-6) synthesized by $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ also exhibited the more ordered smectic A mesophase. The dependence of the degree of polymerization and flexible spacer



Scheme 3.3-6

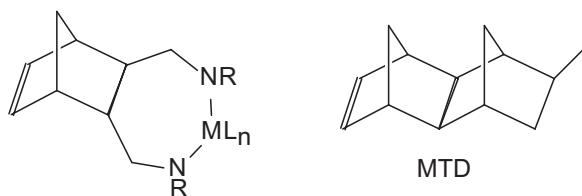


Fig. 3.3-7. Norbornene monomers used for the synthesis of microphase-separated materials.

length on the phase transitions of these systems was determined, demonstrating stabilization of the mesophase by both increasing molecular weight and flexible spacer length.

Schrock has shown that the molybdenum and tungsten catalysts can tolerate main group and transition metal functionalities appended to the norbornene skeleton and has exploited these monomers to prepare low dispersity block copolymers with well-defined microphase-separated regions [73–79]. A type of monomer that has proved particularly effective for carrying metals into microphase-separated materials is the chelating diamide substituted norbornene [73, 76] illustrated in Figure 3.3-7. The morphologies of these copolymers were investigated by transmission electron microscopy (TEM) and small-angle X-ray scattering (SAXS). Depending on the ratio of norbornene to the metal-derivatized bis-amide, materials containing lamellae, cylinders, or spheres of the metal-containing component embedded in polynorbornene can be obtained. For the purpose of film forming and microtoming of samples, the higher T_g polymer arising from methyltetra-cyclododecene (MTD) was found to be superior to polynorbornene [79]. The microphase-separated polymers can then be chemically treated to give aggregates of, for example, semiconductor materials such as ZnS and CdS [76] and nano-clusters of metallic Pd or Pt [78] or Ag or Au [79].

In an alternative method, prefabricated clusters were incorporated within a polymer containing phosphine donors attached to the polymer backbone [80]. Nearly monodispersed CdSe nanoclusters, surface-passivated with a layer of trioctylphosphine and trioctylphosphine oxide, have been sequestered within phosphine-containing domains in a diblock copolymer. Diblock copolymers of phosphine- or phosphine-oxide-functionalized norbornenes (Figure 3.3-8) and MTD were prepared by ROMP using molybdenum-alkylidene initiators. Under desirable conditions, the copolymers underwent microphase separation, and the metal chalcogenide clusters were predominantly sequestered within the phosphine-containing microdomains.

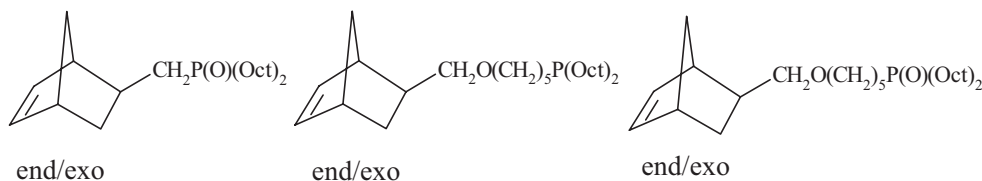


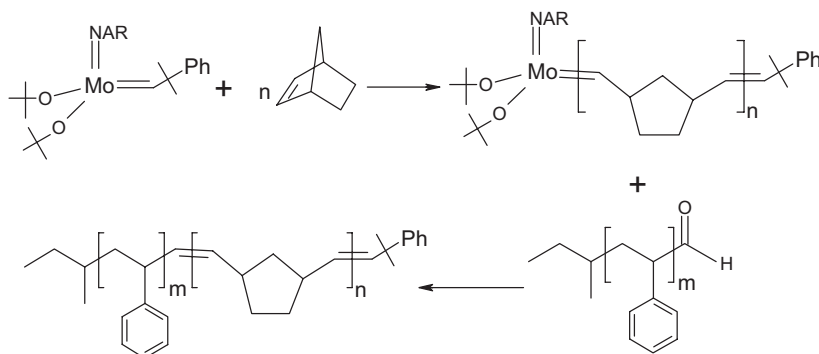
Fig. 3.3-8. Phosphine-containing norbornene monomers.

3.3.3.2

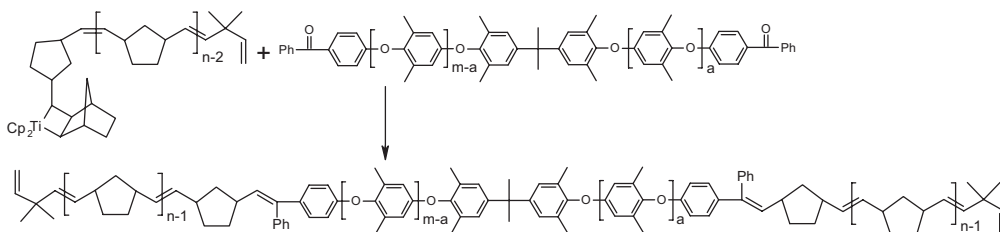
Coupling Reaction

Coupling of living polymers Living polymerizations, such as ROMP, ATRP, group-transfer polymerization (GTP), and anionic polymerization, can produce block copolymers of well-defined architecture and narrow molecular weight distribution. However, each mechanism is effective for only a limited range of monomers, greatly curtailing the diversity of accessible block copolymers. To circumvent this limitation, polymers synthesized by different mechanisms may be end-functionalized with complementary groups and reacted together, though the resulting condensation linkages may limit the stability of the polymers. The combination of well-defined anionic and ROMP to synthesize block copolymers without introducing undesired functionality into the polymer backbone is particularly desirable, as the anionic and ROMP mechanisms operate on non-overlapping classes of monomers and both can produce polymers of very low polydispersity.

Diblocks have been synthesized by preparing ω -aldehyde-functionalized polymers anionically and employing these as macromolecular terminators for ROMP (Scheme 3.3-7) [81]. This approach is based on the Wittig-like coupling of a living ROMP polymer and a carbonyl-bearing moiety, a reaction used previously to generate end functionalization or to couple identical growing chains [82]. In this work Quirk and Kuang's method [83] was used to prepare near monodisperse polystyrene and polyisoprene bearing a single aldehyde functionality at the chain end. All polystyrene-aldehyde (PSA) and polyisoprene-aldehyde (PIA) synthesized possessed polydispersity indices $PDI \leq 1.12$. 1H NMR indicated $>80\%$ aldehyde functionalization in all cases. PSA and PIA were then used as macroterminators to form near-monodisperse diblocks with polynorbornene, poly(ethylidene norbornene), and polycyclopentene. All ROMP reactions were run using Schrock's molybdenum initiator. A 5:1 molar ratio of trimethylphosphine (PMe_3) to $[Mo]$, needed to slow propagation in the cyclopentene polymerization [84], was added in all cases for consistency. PDI of diblock copolymers was 1.03–1.08. However, it should be noted that substantial excesses of polymeric aldehyde have been used to



Scheme 3.3-7



Scheme 3.3-8

promote prompt and complete ROMP termination, requiring subsequent fractionation to isolate pure diblock polymer.

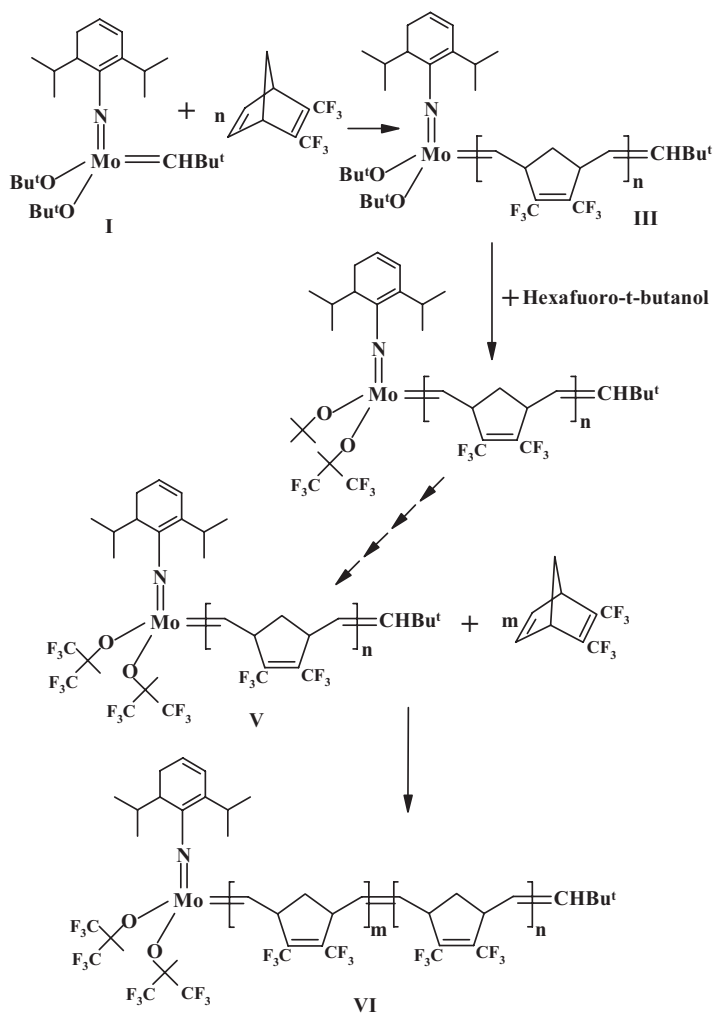
Coupling by Wittig-type reaction Preparation of block copolymers involving the reaction of the end groups of preformed polymer blocks via Wittig-type reaction has been reported [85, 86]. Titanacyclobutane-ended polynorbornene blocks were allowed to react with poly(oxy-2,6-dimethyl-1,4-phenylene) containing two aromatic ketone end groups, and ABA triblock copolymers were obtained (Scheme 3.3-8). The block copolymers exhibited PDI in the range 1.35 to 1.50. According to DSC studies, $(\text{NBE})_{26}(\text{DMP})_{29}(\text{NBE})_{26}$ exhibited one T_g at 70 °C. The miscibility of the two polymer blocks probably results from the low molecular weight of the polynorbornene block. A polymer blend prepared from PNBE with M_n of 6300 and P(DMP) with M_n of 4200 is phase separated and possesses two T_g s at 36 °C (PNBE) and 190 °C (PDMP).

3.3.3.3

Transformation of Propagating Species

The transformation of the polymer chain end into an initiator for a different class of polymerizations permits the synthesis of block copolymers. The living polymerization techniques give a powerful tool for the synthesis of block copolymers with well-defined structures by transformation of a growing chain end to a group capable of initiating polymerization of the second monomer. The method is especially well suited for block copolymers prepared from monomers that polymerize by two different mechanisms.

ROMP to ROMP Living polymerizations can be used to make block copolymers, which allows control of supramolecular organization via the phase separation of incompatible blocks [87]. Blocks derived from the same monomer but having different microstructures may be incompatible, leading to morphology control and hence bulk property control in a material derived from one monomer; such stereoblock copolymers have been prepared via anionic [88] and metallocene [89] methods. It has been demonstrated that this is also possible using ROMP [90]. Poly(BTFMND) was obtained as a stereoblock copolymer containing *cis* and *trans*



Scheme 3.3-9

vinylene blocks via ligand exchange in living stereoselective ROMP initiated by a well-defined Schrock-type initiator (Scheme 3.3-9).

In small-scale trial experiments (NMR tube), initiation of BTFMND (10 equivalents) with well-defined Schrock molybdenum initiator (I) gave living polymer III with a chain end characterized by a doublet in the ^1H NMR spectrum (C_6D_6 solution) at 11.34 ppm arising from the molybdenum alkylidene. After freeze-drying, the residue was treated with a solution of dry hexafluoro-*t*-butanol in dry C_6D_6 for 30 min, freeze-dried, and re-dissolved in C_6D_6 before recording a ^1H NMR spectrum. A further four cycles of the freeze-drying and reaction sequences gave the product V, in which all the alkoxy ligands are hexafluoro-*t*-butyl; this living polymer was used to initiate the polymerization of BTFMND (15 equivalents). The

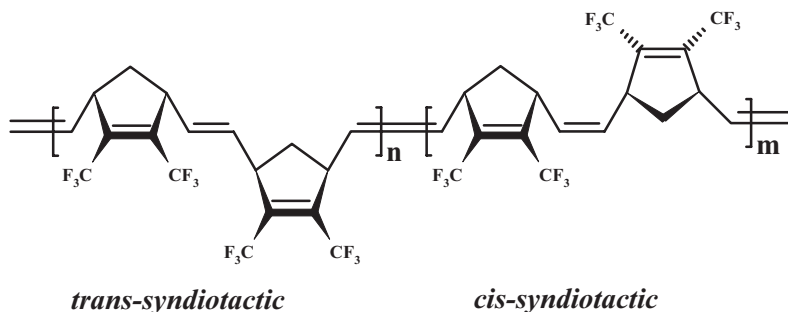
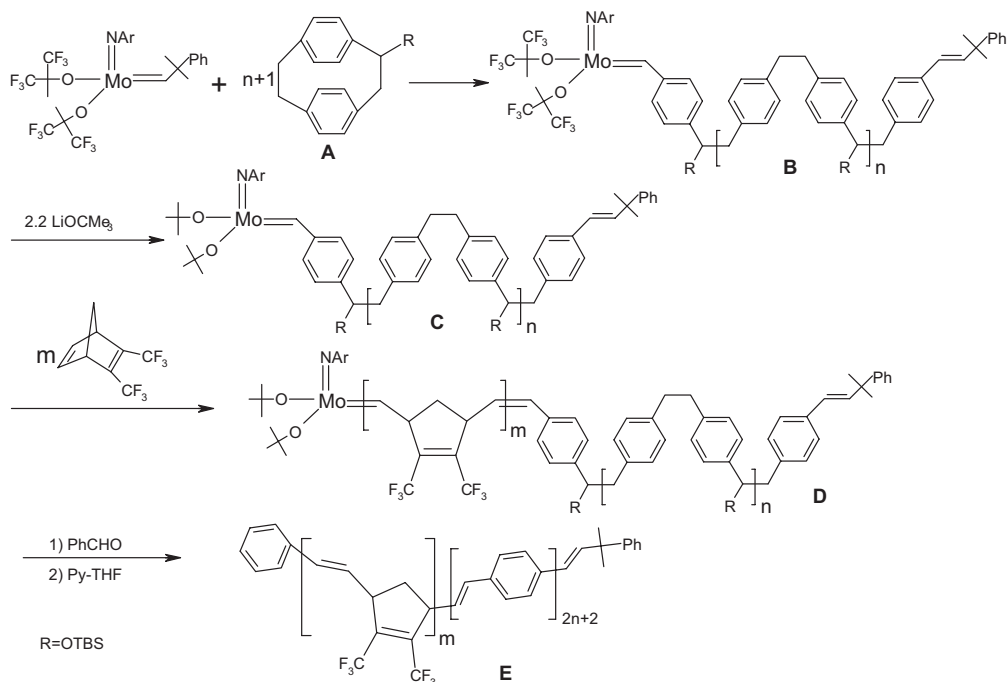


Fig. 3.3-9. Structure of the stereoblock fluoropolymer.

resulting living stereoblock copolymer **VI** was terminated by addition of benzaldehyde (10 equivalents) to give a polymer that displayed all the signals associated with *cis* and *trans* vinylene sequences in blocks of poly(BTFMND). The whole process was repeated on a larger scale (2×100 equivalents of BTFMND). The stereoblock copolymer obtained exhibited M_n of 73,000 and M_w/M_n of 1.16. The polydispersity observed is remarkably narrow, considering the number of steps involved, and is indicative of a very well-defined living polymerization process. The *cis/trans* blocks in the stereoblock copolymer are expected to have the same tacticity as their corresponding homopolymers, as shown in Figure 3.3-9. Differential scanning calorimetry revealed two transitions at ca. 95 °C and 145 °C as expected for the *trans* and *cis* blocks, respectively.

Similarly, encapsulation of emissive polymers within a fluorinated matrix using the alkoxide-ligand exchange strategy has also been reported [91]. The report involves the synthesis of block copolymers containing poly(*p*-phenylenevinylene) (PPV) and *trans-syndiotactic*-poly(BTFMND). PPV exhibits emissive electroluminescence and can be implemented as an emissive material in high-emitting diodes [92]. The fluorinated section has been shown to have, after poling, high relaxed dielectric constant and to demonstrate pyroelectric behavior [93]. Both homopolymers are accessible via ROMP but require different molybdenum-based Schrock-type initiators [94, 95]. PPV is derived from the *cis*-specific living ROMP of **A**, which works only when very active initiators, such as molybdenum hexafluoro alkylidene, are used [96, 97]. Poly(BTFMND) requires an all-*trans*, highly tactic stereochemistry to maximize its pyroelectric properties [64], which is achieved by the less-reactive molybdenum *t*-butoxide alkylidene initiator. The detailed sequence of steps is shown in Scheme 3.3-10. Adding **A** to the hexafluoro molybdenum initiator results in living *cis*-polymer **B**. At this stage, 3–4 equivalents of LiOCMe_3 are added, which completely replace their fluorinated counterparts on molybdenum to generate a new propagating species, **C**. The addition of BTFMND to the reaction mixture results in block copolymer **D**.

The block copolymerization of various combinations of cyclic olefins using the well-defined ruthenium initiators $(\text{PPh}_3)_2\text{Cl}_2\text{Ru}=\text{CHCH}=\text{CPh}_2$ (**1**) and $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHCH}=\text{CPh}_2$ (**2**) has been reported [98]. The living nature of the catalysts allowed control of the formation of di- and triblock copolymers. The poly-



Scheme 3.3-10

merization of norbornene (NBE) by **1** proceeded in a living fashion ($\text{PDI} = 1.27$). The initiator is, however, inactive for the homopolymerization of both cyclopentene (CPE) and COD. Attempted copolymerization of NBE and CPE or COD resulted in only the formation of polyNBE. However, it has been shown that the block copolymerization of two monomers of different reactivity can be accomplished by changing the nature of the propagating species during the polymerization by adding PCy_3 to polymerization mixture using initiator **1**. The exchange of the PPh_3 ligands in **1** with PCy_3 yielded more active initiator **2**, allowing the formation of block copolymers of NBE and 5-acetoxy-1-cyclooctene.

ROMP to Ziegler-Natta polymerization Switching from olefin metathesis to Ziegler-Natta polymerization is of interest in order to prepare block copolymers and to establish the relationship between these two related modes of olefin polymerization. The titanacyclobutanes, catalysts for living ROMP, have been transformed into alkyltitanium complexes, components of catalysts for Ziegler-Natta polymerizations, with the aim of obtaining poly- α -olefin-poly-norbornene copolymers [99, 100]. 3,3-Dimethylcyclopropene-titanacyclobutane, the most effective Ti-based initiator of ROMP, and the chain-propagating titanacycles have been converted into alkoxy derivatives (Figure 3.3-10). $^{13}\text{C}_2\text{H}_4$ polymerizations, catalyzed by these alkyltitanocene alkoxydes in the presence of the AlEtCl_2 co-catalyst, have been monitored by ^{13}C NMR spectroscopy and show that PE can grow on the Ti-alkyl

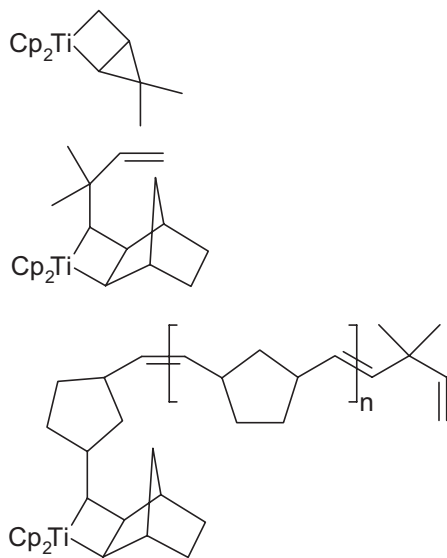
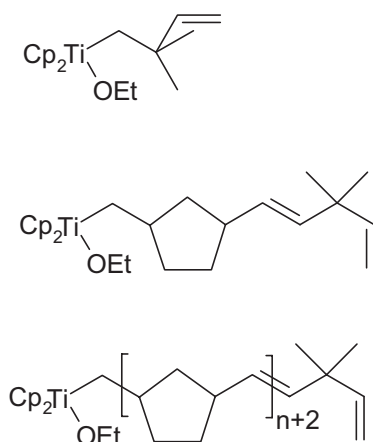
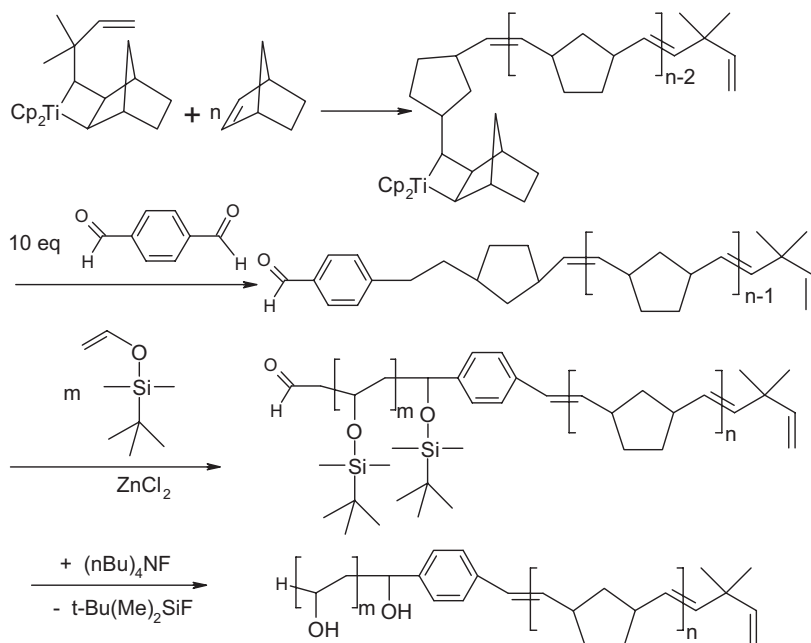
Titanacyclobutane**Alkoxy derivative**

Fig. 3.3-10. Examples of titanacyclobutane complexes and their corresponding alkoxy derivatives, initiators for Ziegler-Natta polymerisation.

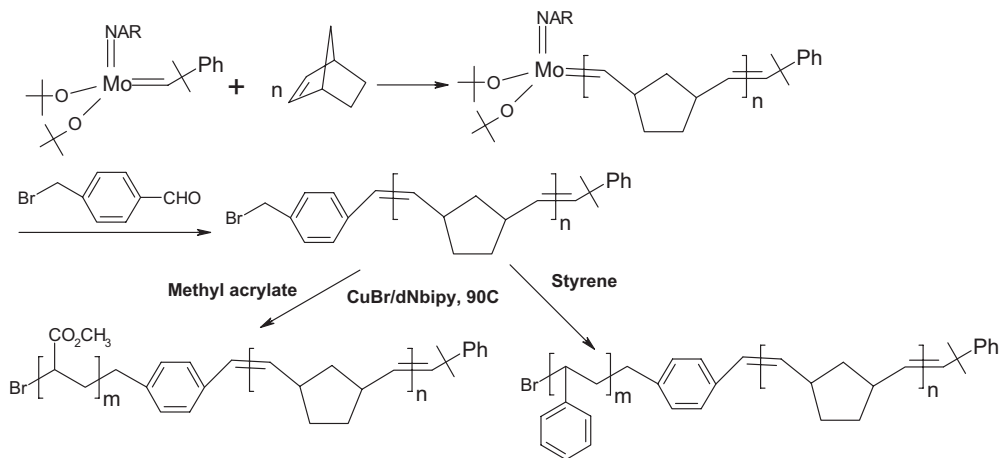
bond derived from the ROMP catalysts. This methodology resulted in the formation of polynorbornene-polyethylene block copolymers.

ROMP to group-transfer polymerization The titanacyclobutane end groups in living polymers react readily with aldehyde derivatives in a Wittig-type reaction. The Wittig-type reaction of titanacyclobutane end groups allowed the preparation of AB-type diblock copolymers by changing from ROMP to group-transfer polymerization (GTP) [101, 102]. The living ROMP of norbornene was terminated with a ninefold excess of terephthalaldehyde; the chains formed carry an aldehyde end group, which was activated by ZnCl₂ and used to initiate the aldol-group-transfer polymerization of tert-butyldimethylsilyl vinyl ether (Scheme 3.3-11). This method has successfully produced polynorbornene-poly(silyl vinyl ether) diblock copolymers with narrow molecular weight distributions (PDI = 1.1–1.6). The cleavage of the silyl groups resulted in hydrophobic-hydrophilic block copolymers with poly(vinyl alcohol) as the second polymer block. DSC analysis revealed phase separation for these block copolymers.

ROMP to ATRP The integration of ROMP with other polymerization methods such as ATRP [103–105], a controlled radical polymerization process, has permitted the preparation of novel block copolymers. A general method of this transformation is reported for the preparation of block copolymers (Scheme 3.3-12). The macroinitiator PNB–C₆H₄–CH₂Br (M_n = 30,520, PDI = 1.09) was prepared by ROMP of norbornene and subsequent Wittig-like reactions with



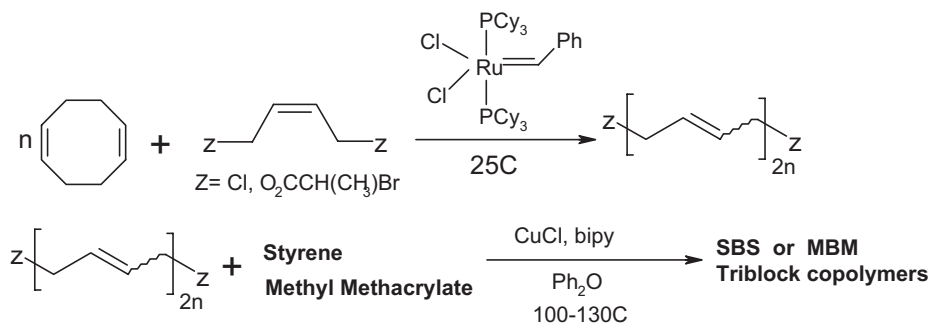
Scheme 3.3-11



Scheme 3.3-12

p -(bromomethyl)benzaldehyde. This compound was used as an efficient macroinitiator for homogenous controlled/living ATRP to prepare block copolymers with styrene ($M_n = 110,400$, $\text{PDI} = 1.06$) and methyl acrylate ($M_n = 85,000$, $\text{PDI} = 1.07$) [106].

While this method was found to be an effective route for preparing diblock copolymers, the synthesis of triblock copolymers requires a telechelic polymer



Scheme 3.3-13

[107] with initiating groups on both ends. The synthesis of poly(styrene)-*b*-poly(butadiene)-*b*-poly(styrene) (SBS) and poly(methylmethacrylate)-*b*-poly(butadiene)-*b*-poly(methylmethacrylate) (MBM) triblock copolymers with poly(butadiene) (PBD) segments containing 100% 1,4-microstructure is described (Scheme 3.3-13) [108]. Bis(allyl chloride)- and bis(2-bromopropionate)-terminated telechelic PBDs were synthesized by ROMP of 1,5-cyclooctadiene in the presence of the corresponding difunctional chain-transfer agents. These telechelic PBDs were subsequently used as difunctional macroinitiators for the heterogeneous ATRP of styrene and methylmethacrylate to form SBS and MBM triblock copolymers. Triblock structures were confirmed by selective PBD degradation. The PDIs were in the range 1.48–1.68.

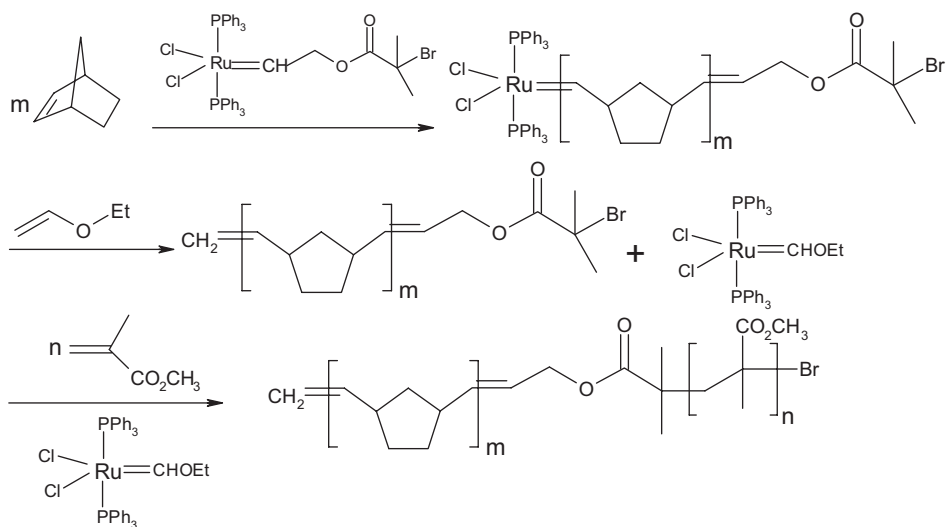
Block copolymers have also been synthesized by using a tailored ruthenium-carbene complex containing an activated carbon-halogen bond able to initiate ATRP [109]. $\text{RuCl}_2(\text{=CHCH}_2\text{-O(O)C-C(CH}_3)_2\text{Br})(\text{PCy}_3)_2$ was prepared from $\text{RuCl}_2(\text{=CHPh})(\text{PCy}_3)_2$ and allyl 2-bromo-2-methylpropanoate and then was allowed to polymerize norbornene in a controlled way. After conversion of the polymer growing chains into the methylene-end-capped polynorbornene and the free $\text{RuCl}_2(\text{=CHOEt})(\text{PCy}_3)_2$ complex, the carbon-bromine termini of the polymer chains served as the initiator of ATRP of methyl methacrylate, yielding the poly(norbornene-*co*-methyl methacrylate) with a narrow molecular weight distribution (Scheme 3.3-14).

3.3.3.4

Application of Well-Defined Bimetallic Initiators

Triblock copolymers have unique physical properties. Many phase-separated block copolymers behave as thermoplastic elastomers or can be used as semi-permeable membranes [110]. The formation of ABA triblock copolymers via a two-step ROMP using bimetallic, well-defined ruthenium initiators (Figure 3.3-11), which is living at both chain ends, has been reported [111].

Reactions of 7-oxanorbornenes or a silicon-containing norbornene (Figure 3.3-12) with the initiator with R = cyclopentyl (3) resulted in polymers with low polydispersities ranging from 1.10 to 1.19, while polymerizations initiated by



Scheme 3.3-14

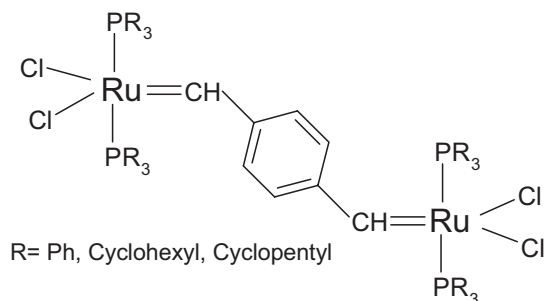


Fig. 3.3-11. Well-defined di-ruthenium initiator.

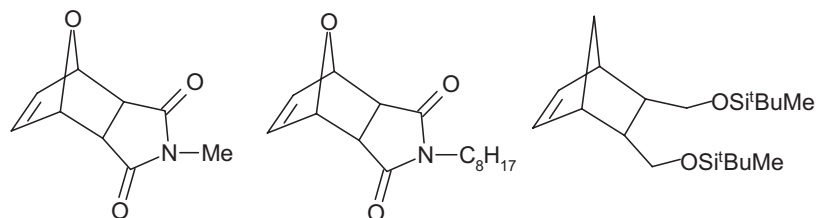


Fig. 3.3-12. Norbornene and oxonorbornene monomers used for the synthesis of ABA block copolymers.

ruthenium complex with R = cyclohexyl (2) displayed higher polydispersities ranging from 1.20 to 1.35. However, the initiator with R = Ph (1) was not reactive enough to polymerize functionalized norbornenes or 7-oxanorbornenes. The living polymerization catalyzed by 2 or 3 was applied to ABA block copolymerization of the monomers shown in Figure 3.3-12. In all cases, the first monomer was poly-

merized to completion, followed by addition of the second or the third monomer. Polydispersity of the triblock copolymers ranged from 1.26 to 1.50.

3.3.4

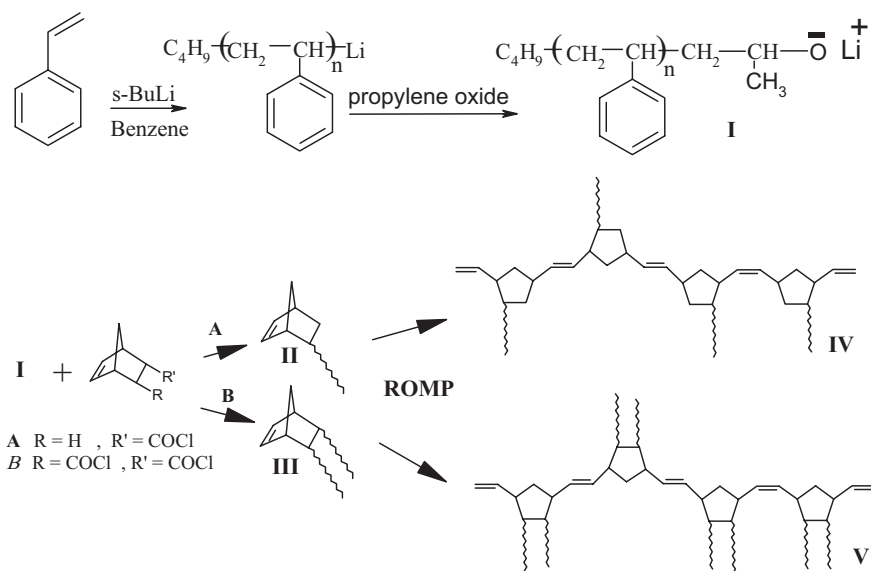
Comb and Graft Copolymer

3.3.4.1

Combination of ROMP and Anionic Polymerization

The potential of combining the capabilities of living anionic and ROMP methods has been explored to prepare polymers with well-defined structures and unusual topologies. This approach offers access to a range of graft copolymers that cannot be prepared by grafting onto or from homopolymer backbones. Additionally and importantly, the method allows rational design and synthesis of graft copolymers with control over the main-chain and graft-chain molecular weights and the graft density.

Well-characterized 5-norbornene-2,3-*trans*-bis(polystyrylcarboxylate) macromonomers, **III**, were synthesized according to Scheme 3.3-15. The ROMP of the macromonomers using well-defined Schrock molybdenum initiators, $\text{Mo}(N\text{-}2,6\text{-}i\text{-Pr}_2\text{C}_6\text{H}_3)(\text{OCMe}_3)_2(\text{CHR})$ where R is CMe_3 or CMe_2Ph , produced well-defined graft copolymers, **V** [112, 113]. The graft copolymers produced consisted of a polynorbornene backbone carrying two polystyrene grafts on each cyclopentane ring. Well-characterized macromonomers and comb graft copolymers with polystyryl grafts with average degrees of polymerization ($\overline{\text{DP}}_n$) of 4, 7, and 9 were successfully



Scheme 3.3-15

produced [112]. The graft copolymers exhibited single-mode molecular weight distributions and narrow polydispersities, typically in the range 1.09 to 1.16. ROMP of macromonomers of different molecular weights, i.e., different polystyrene graft lengths, revealed a limit to the length of the polynorbornene backbone attainable in the graft copolymer, which was related to the length of polystyrene graft in the macromonomer [113]. These results suggested that the graft copolymer backbone chain grows up to a certain length beyond which the ROMP reaction becomes sterically hindered and eventually stops. As the length of polystyrene graft in the macromonomer was increased, the length of polynorbornene backbone attainable in the graft copolymer decreased. The polymerization reactions were demonstrated to be living by producing block and tapered copolymers with the sterically undemanding monomer 2,3-bis(trifluoromethyl)norbornadiene [113].

Well-defined graft copolymers having a polynorbornene backbone chain carrying only one polystyrene graft on each cyclopentane ring have also been prepared. It was anticipated that this would provide a basis for comparison with the results on the synthesis of graft copolymers with two polystyrene grafts in each cyclopentane ring; with only one graft per norbornene repeat unit, the steric hindrance effect was expected to be lower, allowing the formation of graft copolymers with longer grafts and backbone chains. The synthesis of *exo*-5-norbornene-2-(polystyrylcarboxylate) macromonomers, **II**, was carried out in close analogy to the method described previously [112], and the reaction scheme is outlined in Scheme 3.3-15. The well-characterized macromonomers, **II**, were subjected to ROMP using the same Schrock molybdenum initiators to give graft copolymer, **IV** [114]. The ^1H NMR spectrum of the living polymerization reaction mixture showed two broad unresolved signals at 11.44 and 11.62 ppm, characteristic of the hydrogens of the propagating alkylidenes. These signals could be due to head or tail insertion of the macromonomer to the active site, leading to head-tail, tail-tail, or head-head placements of repeat units in the polymer chain. Furthermore, another signal was observed at 11.31 ppm, characteristic of the hydrogen of the initiator alkylidene and indicating that propagation is faster than initiation. The results suggest that, in contrast to two polystyrene grafts on the same norbornene unit, with one polystyrene graft on the norbornene unit, graft copolymers with relatively long backbone and side chains can be prepared, probably as a consequence of lowered steric hindrance. As observed by ^1H NMR, the macromonomer currently under discussion can add head or tail to the propagating chain end, which reduces the steric hindrance at the growing chain end and allows the synthesis of high-molecular-weight graft copolymers.

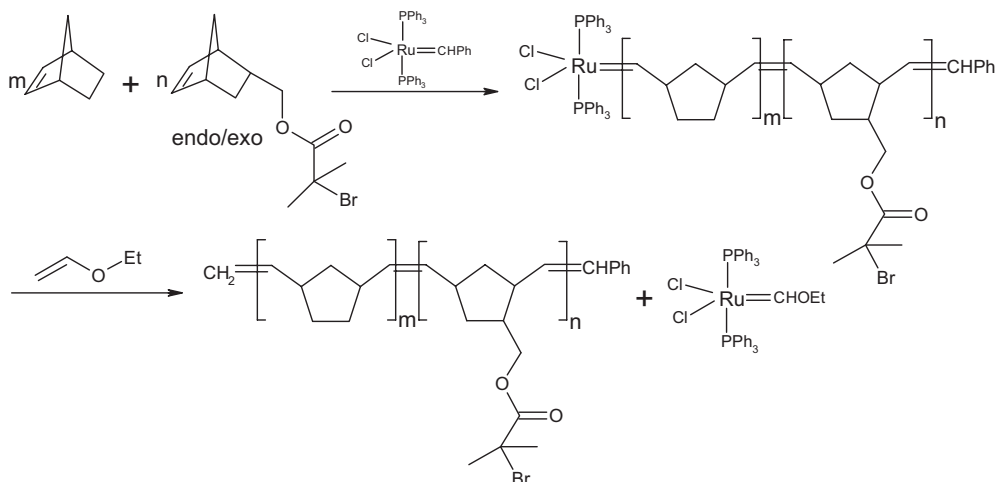
The DSC and TGA results for graft copolymers revealed that in all cases, only one T_g was observed for these graft copolymers. This indicates that the polynorbornene and polystyrene segments do not undergo phase segregation. The T_g of these graft copolymers shows that there is an overall increase in T_g going from graft copolymers containing short polystyrene chains to longer polystyrene chains. The T_g of polynorbornene is 35 °C and that of polystyrene is 100 °C. Thus, the T_g process observed is primarily associated with polystyrene grafts in these systems. A similar trend was observed in relation to thermal decomposition temperatures,

using 2% weight loss as an arbitrary criterion for degradation. As the polystyrene graft length increases, the thermal decomposition temperature also increases.

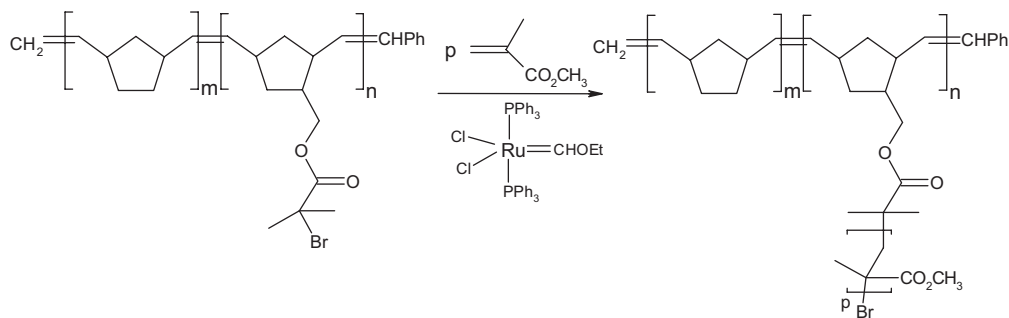
3.3.4.2

Combination of ROMP and ATRP

Graft copolymers have been made by combination of ROMP and ATRP [115–121]. This was achieved by switching the activity of ruthenium complexes from olefin metathesis to ATRP through the conversion of $\text{RuCl}_2(=\text{CHPh})(\text{PPh}_3)_2$, which is a well-known catalyst for the controlled ROMP of norbornene at room temperature, into the corresponding ruthenium-ethoxycarbene complex ($\text{RuCl}_2(=\text{CHOEt})(\text{PPh}_3)_2$), which is inactive at 85 °C (the temperature required for ATRP of methyl methacrylate) toward cyclooctene and the double bonds of polynorbornene, while exhibiting a remarkable efficiency for ATRP of methyl methacrylate, while exhibiting a remarkable efficiency for ATRP of methyl methacrylate. By applying this methodology, poly(norbornene-*g*-methyl methacrylate) copolymers have been prepared by a “grafting-from” technique. In a two-step approach, ring-opening metathesis copolymerization of a mixture of norbornene (NBE) and a norbornene derivative containing an activated carbon-bromine bond (NBE-Br) was carried out first by using $\text{RuCl}_2(=\text{CHPh})(\text{PPh}_3)_2$ as the catalyst (Scheme 3.3-16). The polymerization was terminated upon addition of ethyl vinyl ether (8 equivalents), yielding poly(NBE-*co*-NBE-Br) chains end capped with a methylene group and the corresponding ruthenium-ethoxycarbene complex. Thus, well-controlled polynorbornene containing 4% brominated pendant groups was synthesized ($M_w/M_n = 1.08$). In the next step, the copolymer obtained was used as a macroinitiator for the ATRP of methyl methacrylate using the freshly prepared $\text{RuCl}_2(=\text{CHOEt})(\text{PPh}_3)_2$ complex (Scheme 3.3-17). The resulting graft copolymers ($M_n = 75,000\text{--}150,000$) were obtained in high yields and with narrow molecular weight distributions ($M_w/M_n = 1.25\text{--}1.35$).



Scheme 3.3-16



Scheme 3.3-17

The sequential one-pot synthesis of the same graft copolymer also proved successful, but it required the optimization of some experimental parameters such as the reaction time for the copolymerization of both norbornene and its brominated derivative and the conversion of the copolymer growing chains ($\text{RuCl}_2[=\text{CH-poly}(\text{NBE-co-NBE-Br})](\text{PPh}_3)_2$) into the methylene-end-capped poly(NBE-co-NBE-Br) and the free $\text{RuCl}_2(=\text{CHOEt})(\text{PPh}_3)_2$ complex.

Ruthenium-alkoxycarbene complexes were inefficient for the controlled ATRP of styrene and *n*-butyl acrylate. Therefore, the strategy developed above could not be extended to the synthesis of controlled poly(norbornene-*g*-styrene) and poly(norbornene-*g*-*n*-butyl acrylate) copolymers. However, the controlled synthesis of poly(norbornene-*g*-styrene) could be achieved in a two-step approach using the poly(NBE-co-NBE-Br) macroinitiator in conjunction with typical catalyst systems for ATRP, such as $\text{NiBr}_2(\text{PPh}_3)_2$. The controlled synthesis of poly(norbornene-*g*-*n*-butyl acrylate) started from the same poly(NBE-co-NBE-Br) macroinitiator and took advantage of the high efficiency displayed by $\text{Ru}(\text{Cp}^*)\text{Cl}(\text{PPh}_3)_2$ ($\text{Cp}^* = \text{pentamethylcyclopentadienyl}$) in the polymerization of acrylates. The final graft copolymers were produced with narrow molecular weight distributions ($M_w/M_n = 1.2\text{--}1.3$).

3.3.4.3

Combination of ROMP and Cationic Polymerization

The synthesis of hybrid copolymers of polyphosphazenes with organic polymers is an important objective in both fundamental and applied research. In many cases the physical, mechanical, and electronic properties of a material can be altered through adjustments to the ratio of the copolymer's individual components. Thus, many of the valuable properties of polyphosphazenes can be incorporated into an organic polymer without sacrificing the overall mechanical properties of the materials. The range of physical and chemical properties associated with polyphosphazenes includes elasticity, fire resistance, and solid polymer electrolyte behavior [122, 123]. Mono- and dinorbornenyl telechelic polyphosphazenes (Figure 3.3-13) were synthesized via an ambient temperature living cationic polymerization process [124]. The length of the polyphosphazene chain was easily con-

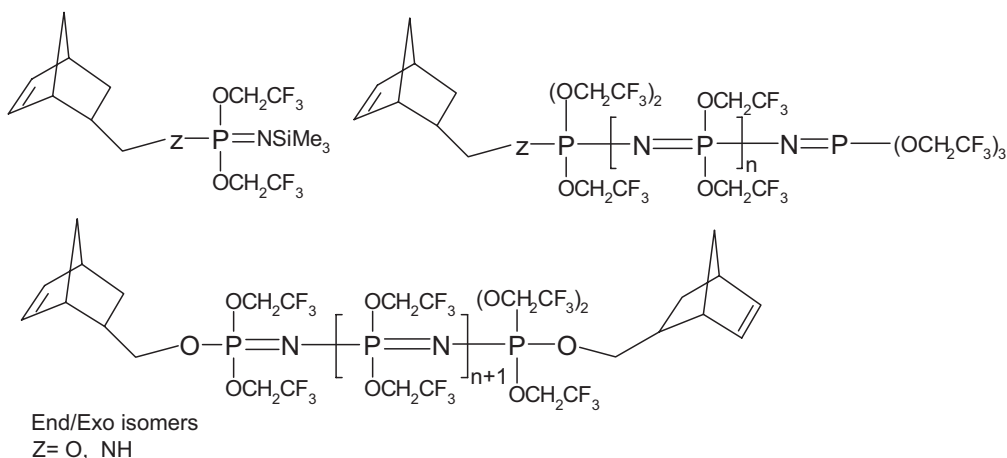


Fig. 3.3-13. Mono- and di-telechelic polyphosphazenes norbornenes.

trolled to produce telechelic polymers with well-defined molecular weights and narrow polydispersities. ROMP of the monotelechelic polyphosphazenes gave soluble graft copolymers. The ditelechelic polyphosphazenes produced cross-linked materials when subjected to ROMP using $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ and $\text{Mo}(=\text{CHCMe}_3)(=\text{NAR})[\text{OCMe}(\text{CF}_3)_2]_2$ initiators. It should be noted that neither the mono- nor ditelechelic macromonomers with $\text{Z} = \text{NH}$ underwent ROMP reactions when treated with either initiators. This was attributed to coordination of the amino groups to the metal center of the initiator.

3.3.4.4

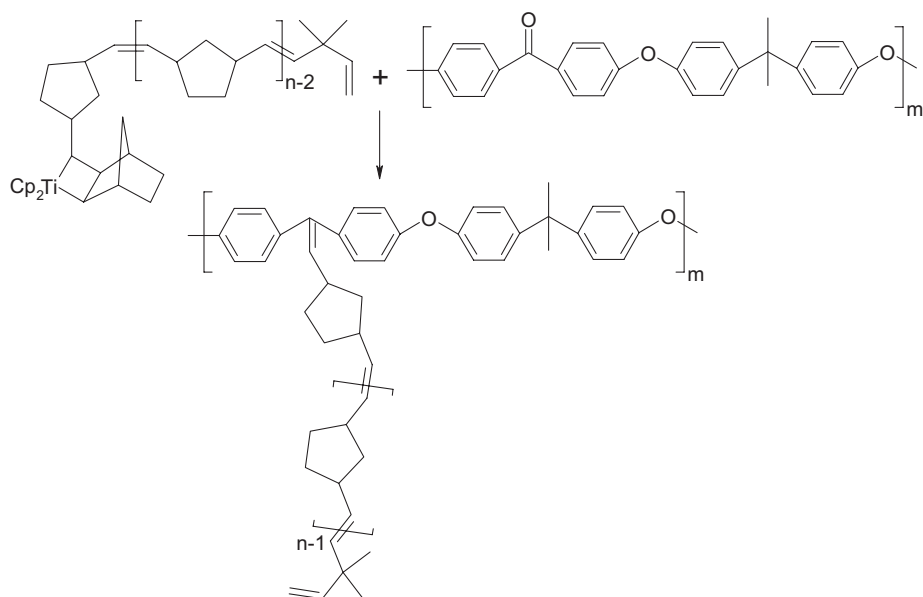
Combination of ROMP and Wittig-Type Reaction

Preparation of graft copolymers involving the reaction of the end groups of pre-formed polymer blocks via Wittig-type reaction has also been reported [85, 86]. Polynorbornene and poly(exo-dicyclopentadiene) with one titanacyclobutane end group were linked in a Wittig-type reaction with polymeric ketone groups such as poly(ether-ketone), producing graft copolymers containing polynorbornene side chains (Scheme 3.3-18). The graft copolymers exhibit PDI in the range 1.35 to 1.50.

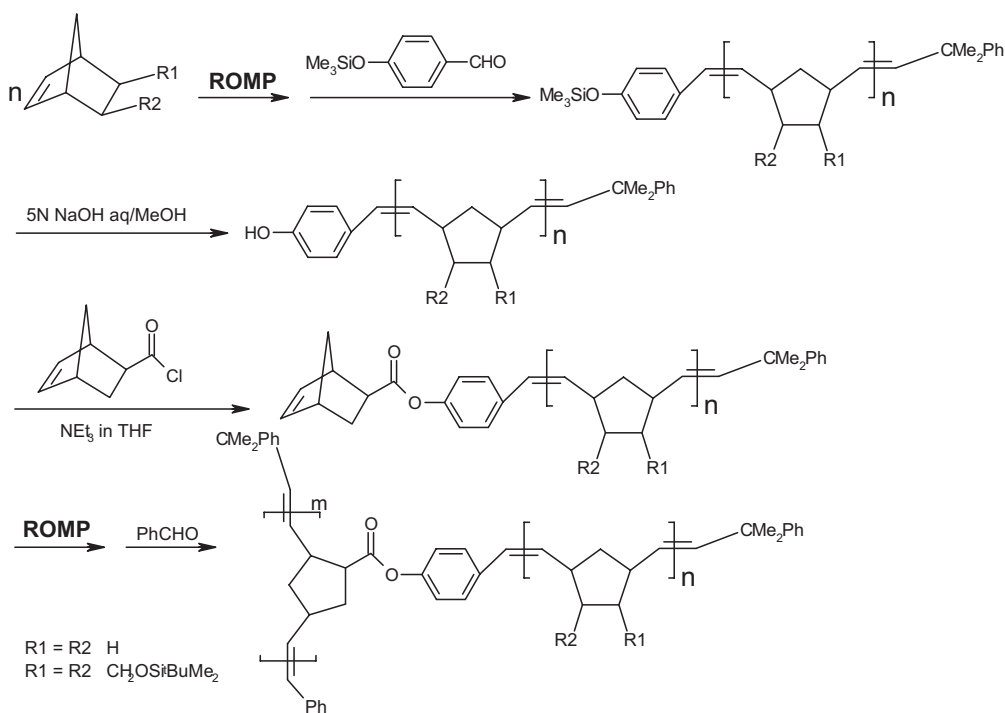
3.3.4.5

Repetitive ROMP

Graft copolymers have been produced that contain ROMP polymers in the backbone chains and side chains. The methodology used was based on repetitive ROMP reactions using well defined molybdenum initiator of the type $\text{Mo}(\text{CHCMe}_2\text{Ph})(\text{N}-2,6\text{-}^i\text{Pr}_2\text{C}_6\text{H}_3)(\text{OR})_2$ [$\text{OR} = \text{OCMe}_3$, $\text{OCMe}(\text{CF}_3)_2$] (Scheme 3.3-19) [125]. It was found that the graft copolymers prepared by molybdenum initiator with $\text{OR} = \text{OR} = \text{OCMe}_3$ showed broad, bimodal molecular weight distribution and that the



Scheme 3.3-18



Scheme 3.3-19

initiator with $\text{OCMe}(\text{CF}_3)_2$ was more suited to this type of chemistry. The observed difference was attributed to the different propagation rates and different reactivities of the two initiators. Various amphiphilic block copolymers have also been prepared by this technique.

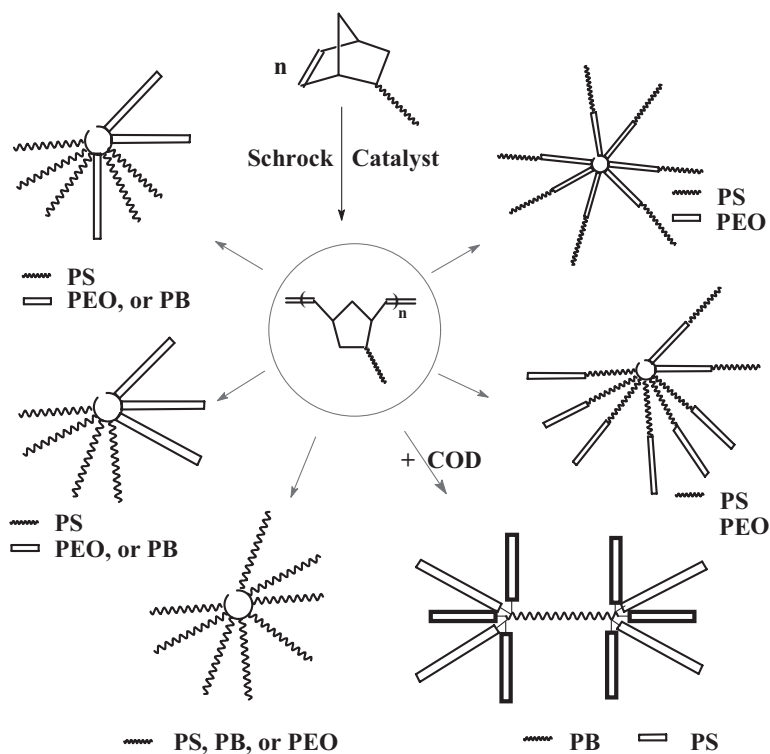
3.3.5

Multi-Shaped Copolymers

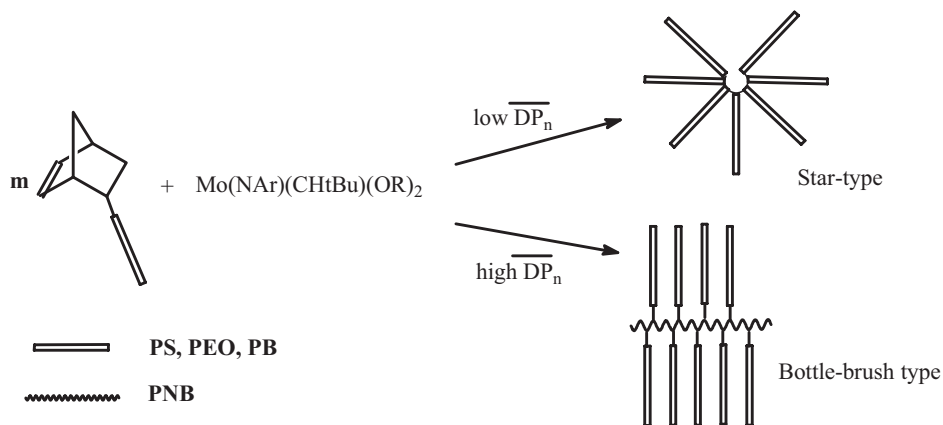
Nonlinear architectures whose branching points are topologically controlled can indeed be shaped in particular forms such as spheres, bottlebrushes, unimolecular micelles, Janus-type spheres, etc. Copolymers with nonlinear- and for some of them asymmetric-structures also attract much interest because features such as their phase diagram and the morphology of their mesophases totally differ from those encountered with linear copolymers. For a long time, anionic polymerization was the only viable process to engineer sophisticated polymeric structures. The ROMP of cycloolefins has emerged as a powerful tool for macromolecular engineering.

Methods have been developed to synthesize nonlinear polymers and copolymers based on polystyrene (PS), poly(ethylene oxide) (PEO), and polybutadiene (PB) by ROMP (Scheme 3.3-20) [126–135]. It was demonstrated that norbornenyl macromonomers could be polymerized under truly living conditions via ROMP. Provided that the macromonomers are end capped with a norbornene molecule, polymacromonomer samples of controlled size and varying compactness can be synthesized using well-defined molybdenum Schrock complexes as initiator. Depending on the length of the macromonomer and the degree of polymerization, ($\overline{\text{DP}}_n$) of the polymacromonomer different topologies, from spheric to flexible cylinders, could be obtained. By this method, polymers with Janus-type, sphere-type, or bottlebrush-type shapes or dumbbell-like, palm-tree-like contours were derived with excellent control and precise topological features.

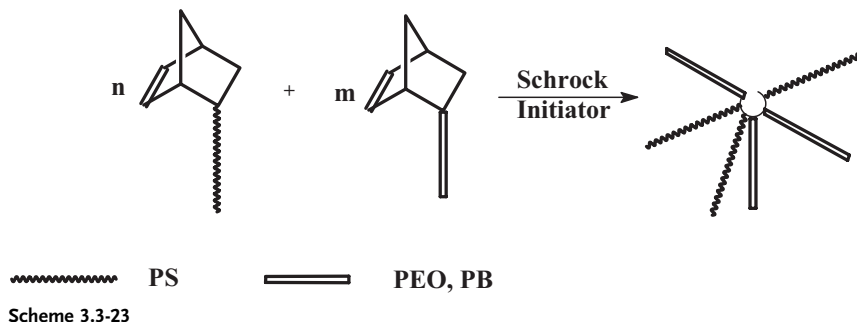
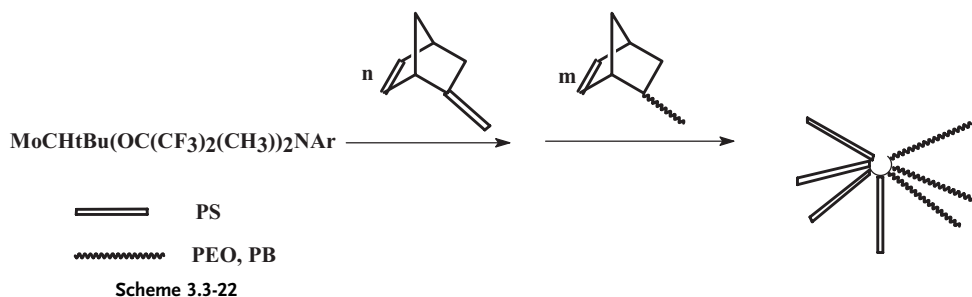
Polymacromonomers of polystyrene (PS), poly(ethylene oxide) (PEO) and polybutadiene (PB) were prepared [126, 133] by ROMP of various norbornene-terminated macromonomers. Complete conversions were achieved, regardless of the $\overline{\text{DP}}_n$ targeted, resulting in polymacromonomers exhibiting low polydispersity indices and experimental molar masses in good agreement with the expected values. In the particular case of ROMP of PB macromonomer [131], the polymerization occurred under controlled conditions, provided that the 1,2-vinyl content was low. When the latter was present in high amounts, norbornene was given little chance to polymerize to completion due to the interference to 1,2-vinyl unsaturations. The viscometry study carried out on PS polymacromonomers showed that the latter exhibited different shapes [134]. As long as the backbone of polymacromonomer remained small, it adopted a spherical shape that progressively moves towards a less-compact bottlebrush shape when the $\overline{\text{DP}}_n$ increases (Scheme 3.3-21).



Scheme 3.3-20



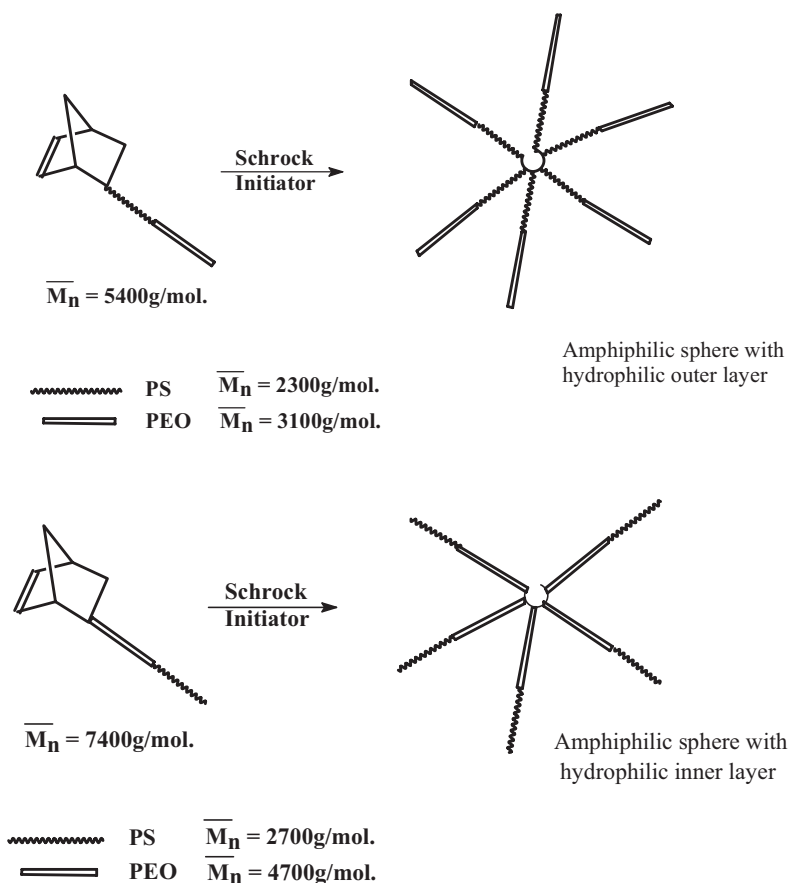
Scheme 3.3-21



The synthesis of polymers exhibiting a globular shape and symmetrical external faces is not an easy task, and the only examples known are the dendrimers prepared by Fréchet et al. The sequential polymerization of two different incompatible norbornene-terminated macromonomers was shown to give rise to Janus-type architectures, under far easier conditions than those required for the synthesis of dendrimers. Two kinds of well-defined copolymers were synthesized by sequential ROMP of PS and PEO or PB macromonomers [129, 134]. The strategy used to obtain the expected architecture is illustrated in Scheme 3.3-22. The order of polymerization of macromonomers appeared to be essential for a complete crossover to occur and indeed gave rise to propagating species of highest reactivity.

Heteroarmed polymacromonomers including PS and PEO or PS and PB arms have been prepared by statistical ROM copolymerization of PS/PEO or PS/PB macromonomers (Scheme 3.3-23) [129, 132, 133]. In all cases, complete conversion of both macromonomers was achieved as confirmed by SEC. The experimental molar masses were found in rather good agreement with the expected values. To know whether the copolymerization of the two macromonomers occurred randomly or exhibited a tendency to blockiness, it would have been necessary to determine the reactivity ratios. However, the observation of only one glass transition ($T_g = 40^\circ\text{C}$) of poly((norbornenyl PS)-co-(norbornenyl PB)) and the perfect alignment of SEC traces arising from UV and RI detectors of poly((norbornenyl PS)-co-(norbornenyl PEO)) indicate the random distribution of PS, PB, and PEO grafts along the polynorbornene backbone.

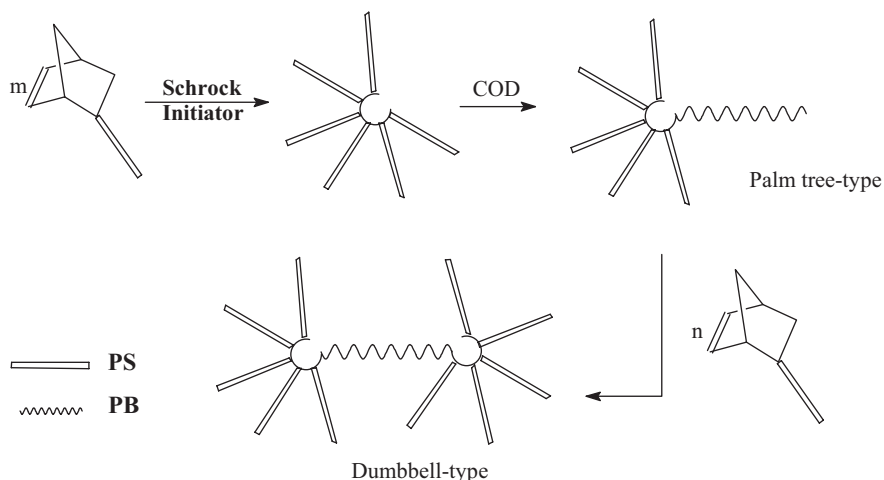
Stars whose arms are block copolymers were obtained by two methods, either by



Scheme 3.3-24

linking a given number of linear chains to a central core or by growing branches from an active core [132]. Exploiting the versatility of the ROMP of norbornenyl macromonomers, star-shaped block copolymers have been obtained by homopolymerization of block copolymers fitted with norbornenyl unsaturations. By ROMP of norbornenyl-(PS-*b*-PEO) macromonomers, amphiphilic spheres with hydrophilic or hydrophobic outer layers have been synthesized (Scheme 3.3-24). The peculiar topology of these polymacromonomers makes them particularly suitable for applications such as unimolecular micelles or associative thickeners. Similarly, compact structures with inner or outer soft phases have been obtained by ROMP of norbornenyl (PS-*b*-PB) macromonomer. The presence of a PS block, even of a very short length, between the polynorbornene backbone and the PB side chain helped to prevent side reactions involving 1,2 vinyl unsaturations.

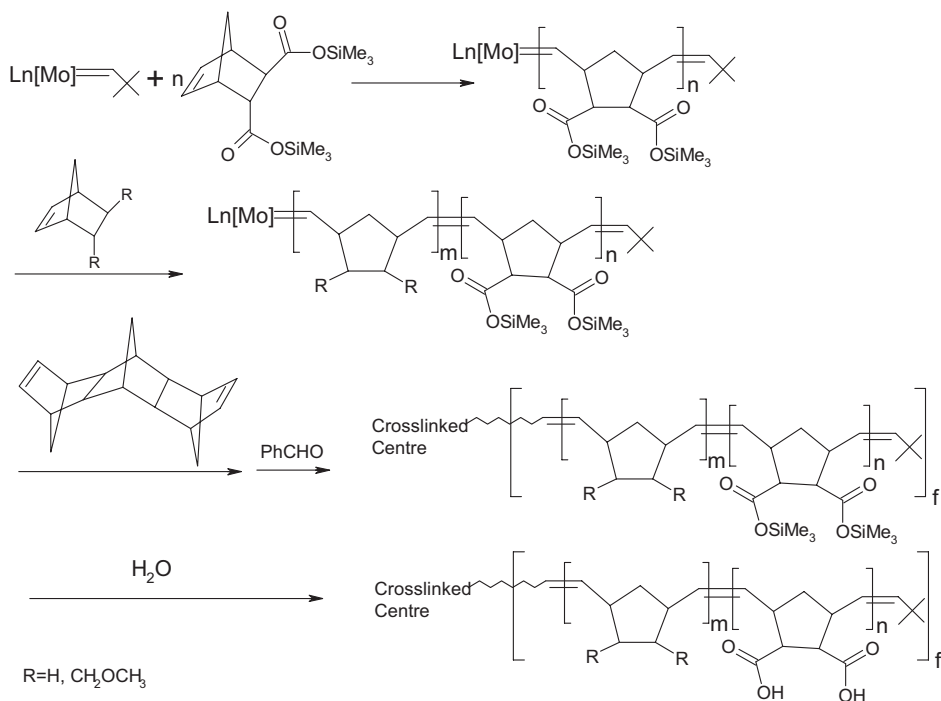
The so-called palm tree-like copolymers consist in an arrangement of n B blocks with one A block of much larger size in a heteroarmed star architecture [133]. These architectures were obtained by sequential copolymerization of norbornenyl-



Scheme 3.3-25

PS macromonomers with a molecular comonomer, namely, cyclooctadiene (COD) (Scheme 3.3-25). Dumbbell-shaped copolymers can be viewed as double stars that are linked through a linear block. They are obtained upon using palm tree-like copolymers to trigger the polymerization of a new amount of PS macromonomers. Four palm tree-like copolymers were prepared. The complete conversion of macromonomer could be confirmed by SEC before the addition of COD. The distribution of molar masses of these palm tree-like copolymers was large, reflecting the slow initiation rate of cycloolefin by the living alkylidene species carried by PS macromonomers. Furthermore, the use of macromonomers of large size resulted in ill-defined samples with a non-negligible proportion of PS polymacromonomer that was found to be unable to initiate the polymerization of COD.

Star-shaped macromolecules have been the subject of many investigations. The synthesis of star polymers by ROMP was reported using a well-defined molybdenum initiator and a cross-linking agent [136]. Furthermore, amphiphilic star-block copolymers have also been prepared by ROMP that consists of a hydrophobic “core” and hydrophilic “shell” employing bis(trimethylsilyl norborne-5-ene)-2,3-dicarboxylate as one of the monomers [137]. The (trimethylsilyl norborne-5-ene)-2,3-dicarboxylate monomer was first added to the molybdenum initiator, followed by norbornene to make the hydrophobic block. The living diblock is then treated with 5–6 equivalents of dinorbornene cross-linking agent to form a star polymer (Scheme 3.3-26). The trimethylsilyl esters were converted to carboxylic acids by soaking the cast film of the polymer in water in 2–3 days. The end product then has a hydrophobic core of polynorbornene and a hydrophilic outer layer. The method was used to prepare a variety of stars with functional groups in the shell, in the core, or in both, to suit whatever application is desired. Uniform, low polydispersity stars were obtained, provided that the right ratio of blocks and block lengths was targeted. On further investigation of these materials, two competing factors were noticed; more uniform, monodisperse stars can be made by lowering



Scheme 3.3-26

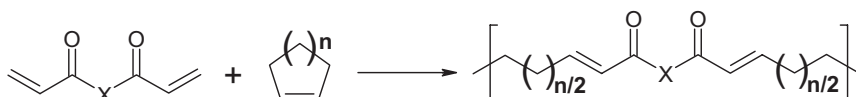
the percentage of the hydrophilic portion, but water solubility requires increasing the hydrophilic portion.

3.3.6

Alternating Copolymers

Alternating copolymers are normally formed by step-growth polymerization of AA-BB monomers and, in some cases, by chain-growth polymerization [47, 138]. Although recent developments in ROMP and ADMET have extended the versatility of both chain-growth and step-growth reactions, these metathesis polymerizations have not provided a general solution to alternating copolymerization. Examples of alternating copolymers by ROMP are rare due to the difficulty of finding systems in which there is an alternation in the affinity of the propagating metal carbene for the monomers [139, 141]. Therefore, a general metathesis route toward A,B-alternating copolymers would open the way to the synthesis of new functional polymers.

Recently, a new and general method for synthesizing highly alternating copolymers by ring-opening insertion metathesis polymerization (ROIMP) has been demonstrated [142]. In this systems the diacrylate monomers are selectively inserted into ROMP polyolefins to yield alternating copolymers (Scheme 3.3-27).



Scheme 3.3-27

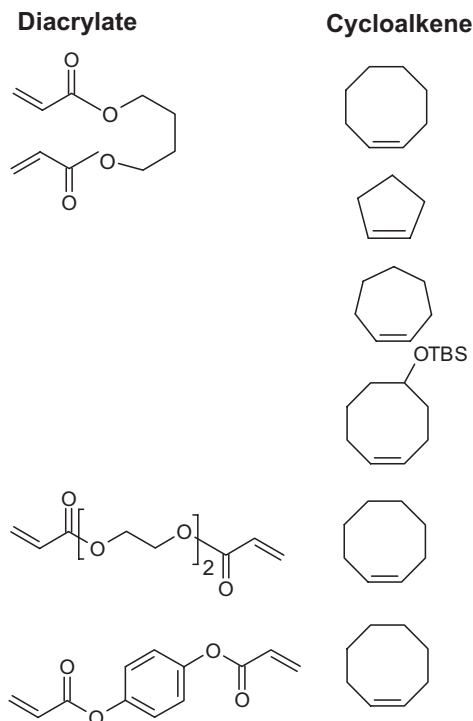


Fig. 3.3-14. Diacrylates and cycloalkenes used for ROIMP reactions.

Treatment of a 1:1 mixture of monomers diacrylates (A) and cycloalkenes (B) with catalyst $(\text{PCy}_3)(\text{DHIMes})\text{Cl}_2\text{Ru}=\text{CHPh}$ yielded highly A,B-alternating copolymers in high isolated yields. Examples of A,B-alternating copolymers from a variety of diacrylates and cycloalkenes are shown in Figure 3.3-14. The high conversion and degree of alternation arise from the thermodynamically driven selective bond formation between diacrylates and cycloalkenes. The extent of A,B-alternation has been determined by ^1H and ^{13}C NMR.

Copolymers such as poly(ethylene-propylene) and poly(ethylene-styrene) represent important classes of copolymers that can be synthesized by Ziegler-Natta polymerization of a mixture of the two monomers [143, 144]. Although some successful examples of the synthetically perfectly alternating CO and styrene copolymers were reported recently [145–147], it has not been possible to insert two similar monomers in an alternating fashion to yield polymers with high regioselectivities (i.e., high head-to-tail regularity). In general, the synthesis of

perfectly alternating copolymers remains a synthetic challenge. For this reason, monomers 3-methylcyclobutene (1) and 3,3-dimethylcyclobutene (2) were polymerized by well-defined hexafluoro molybdenum neopentylidene initiator to give polymers that upon hydrogenation are equivalent to alternating copolymers of poly(ethylene-alt-propylene) and poly(ethylene-alt-isobutylene), respectively [148]. Monomer 2 was polymerized in a highly regioselective fashion to give polymers with exclusively *trans* and head-to-tail configuration. The high regioselectivity of the polymerization is attributed to the steric directing effect of the bulky substituent on the 3-position of the cyclobutene as the monomer approaches the propagating alkylidenes. In the presence of PPhMe₂, poly(3-methylcyclobutene) with narrow PDI was obtained.

Examples of alternating ring-opening metathesis copolymerization have been reported that incorporate polar and non-polar monomers [149]. The results from copolymerization of polar 2,3-difunctionalized 7-oxanorbornene derivatives with a series of non-polar cyclic olefins (cyclooctene, COD, cyclopentene, NBE) using as initiators RuCl₂(=CHPh)(PCy₃)₂ (1) and its mono-1,3-dimesitylimidazolidene-2-ylidene derivative (2) are reported (Figure 3.3-15). The resulting polymer microstructures have been analyzed by ¹H, ¹³C, and ¹H-¹H COSY NMR spectroscopies. Highly alternating structures were observed with initiator 1. The use of initiator 2 resulted in lower levels of alternation with a tendency toward random polymerization.

3.3.7

Cross-Linked Copolymers

3.3.7.1

Well-Defined, Cross-Linked System via Direct Copolymerization

Dicyclopentadiene (DCPD) is cheap and can be polymerized by ring-opening metathesis polymerization (ROMP), which yields a cross-linked polymer. This polymerization process can be tailored to have the characteristics that make it readily adaptable to either reaction injection molding (RIM) or resin transfer molding (RTM). The production of large molded objects from DCPD-based feeds using RIM technology was developed mainly in the U.S. by BF Goodrich under the trade name Telene and by Hercules under the trade name Metton [150–160]. The advantages of DCPD include a rapid reaction (good for RIM and RTM) and good product mechanical properties, including low density, low water absorption, and excellent toughness. The disadvantages include a nasty smell, an exothermic reaction that can be difficult to control, and the difficulty of regulating the cross-linking reaction, which reduces the processability and the range of mechanical properties available.

Recently, a process has been developed that involves ROMP-RTM copolymerization of mono- and difunctional monomers to produce well-defined cross-linked polymers (Figure 3.3-16) [161–165]. This kind of in-mold processing requires

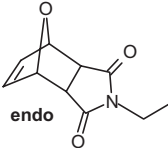

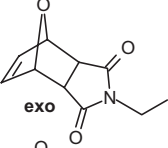

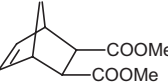

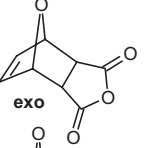

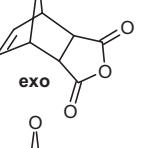

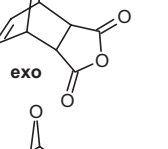

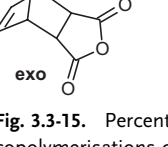

Monomer Systems	Catalyst 1	Catalyst 2
 endo		98 85
 exo		80 70
 COOMe COOMe		91 60
 exo		96 75
 exo		92 -
 exo		85 70
 exo		40 -

Fig. 3.3-15. Percentage of alternating diads resulting from the copolymerisations of different monomer combinations for catalysts 1 and 2.

a high conversion of monomers, since incomplete reaction, and particularly residual monomer, will affect the physical and thermal properties of the product. This system provides control over the degree of cross-linking through the addition of the amount of the difunctional monomer. A crucial factor in the development of the synthesis route was the availability of the ruthenium initiator, $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$, developed by Grubbs et al. The advantages of this initiator over others include its stability toward functional groups and water, the possibility of well-controlled living polymerization, and its solubility in the monomers.

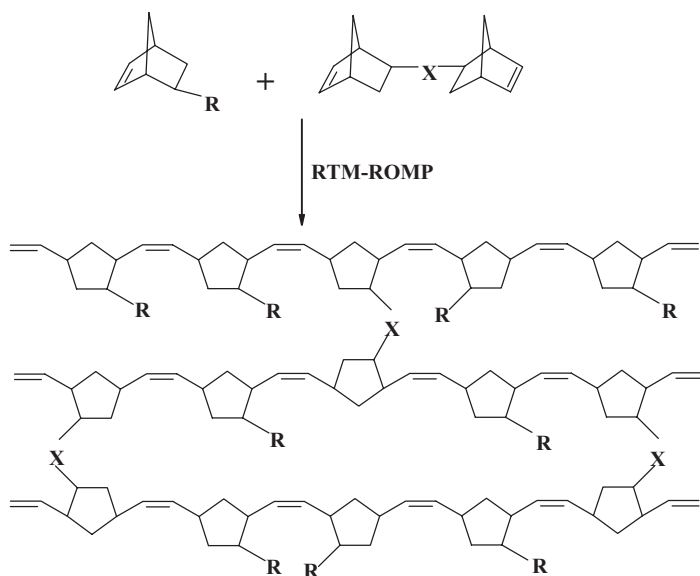
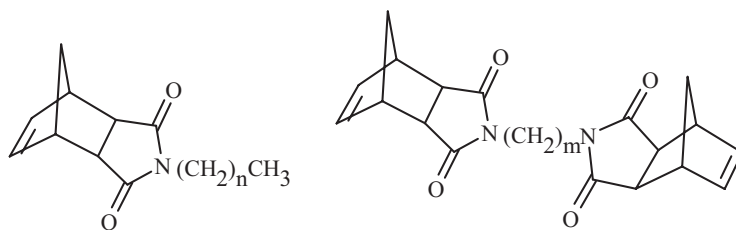


Fig. 3.3-16. RTM-ROMP processing of mono- and di-functional norbornene derivatives giving rise to the synthesis of well-defined crosslinked polymers.



a) Monofunctional monomer - CnM

b) Difunctional monomer - CmD

Fig. 3.3-17. Monofunctional *N*-alkyldicarboxyimidonorbornenes and difunctional bis(*N*-alkylenedicarboxyimidonorbornenes) monomers.

Two types of monomers were used, both based on *N*-alkyl norbornene dicarboxyimide. Monofunctional *N*-alkyldicarboxyimidonorbornenes, termed CnM, carrying pendant alkyl chains of different lengths (Figure 3.3-17a). The monomer was synthesized in both endo and exo forms. The exo isomers were preferred because they were much more reactive than their endo analogues. The monofunctional monomers synthesized included $n = 3, 4$, and 5 . The second type of monomers synthesized for this study were difunctional bis(*N*-alkylenedicarboxyimidonorbornenes) with an alkylene spacer (Figure 3.3-17b). These materials, termed CmD, were synthesized for values of $m = 3, 5, 6, 9$, and 12 . Monofunctional *N*-alkyldicarboxyimidonorbornenes were polymerized using RTM-ROMP processing to give linear

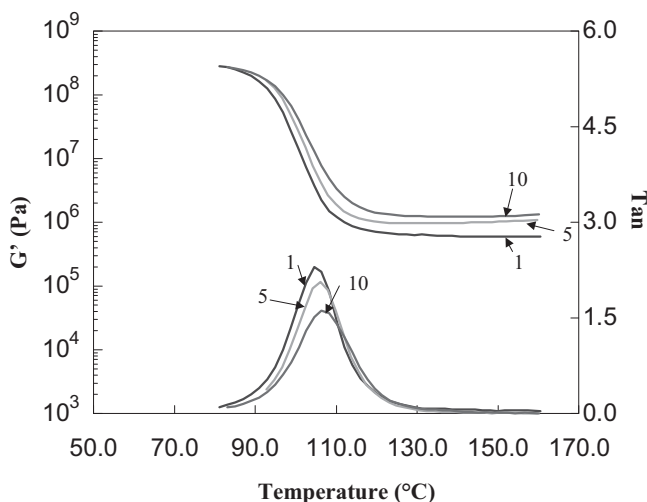


Fig. 3.3-18. Dynamic torsion results for C5M + x mole percent of C12D: x = 1, 5 and 10.

polymers. The difunctional bis(*N*-alkylenedicarboxyimidonorbornenes) were copolymerized with the monofunctional monomers to produce cross-linked polymers using the same processing method.

Dynamic mechanical analysis (DMA) was employed to examine the variation in relaxation behavior, particularly the glass transition temperature T_g , with side chain length. DMA also proved to be a useful way of establishing the optimum processing conditions and of investigating the effects of molecular architecture (for example, the side-chain length and the cross-link spacer length) on mechanical properties. Particular attention was given to measurements of the shear modulus above the glass transition temperature. This was used to determine a value for the molecular weight between cross-links, using simple rubber elasticity theory [166], and the results were compared to those expected from the stoichiometry of the monomer mixture. The results showed that the optimum M:I ratio for the C5M/CmD system was 8000:1. Having established this fact, a range of samples was prepared using this ratio to investigate the effect of varying the percentage of the difunctional component and the length of the difunctional linkage. Figure 3.3-18 shows the dynamic shear modulus results for the C5M/C12D combination, with 1, 5, and 10 molar percentage of the difunctional component. The results show that as the percentage of the difunctional, cross-linking unit is increased, the glass transition shifts to a higher temperature, the height of the $\tan \delta$ peak decreases, and the plateau shear modulus above T_g increases. These results are as expected for an increase in the cross-link density of a polymer. In his review of the cross-linking effect on the physical properties of polymers, Nielsen [167] describes these three effects. The system reported in this work turns out to be a textbook example of a well-defined and homogeneously cross-linked system.

The most interesting aspect of these dynamic torsion results is that they can be used to obtain a measure of the cross-link density of the synthesized polymers.

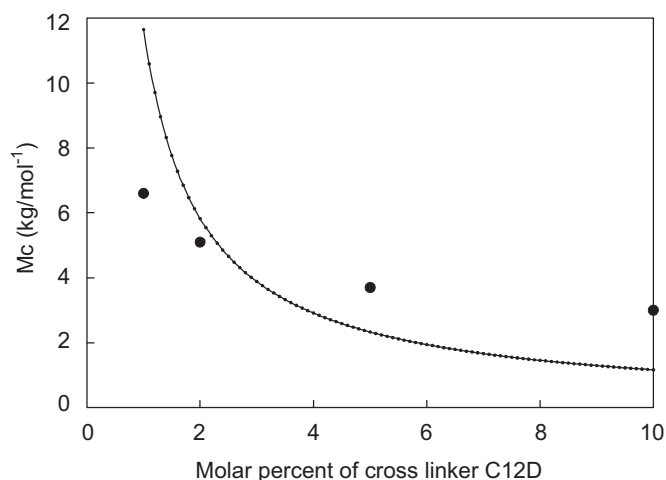


Fig. 3.3-19. A comparison of the theoretical molecular weight between crosslinks (solid line) with the calculated value (●), for the C5M/C12D polymer.

Tab. 3.3-1. The mechanical properties of the crosslinked polymers.

System	T_g (°C)	Density kg m^{-3}	Modulus GPa	Yield/Fracture strength (MPa)
C4M/2% C12D	~120	1136	2.7 ± 0.2	61 ± 15 (F)
C5M/2% C12D	106	1120	2.2 ± 0.2	72 ± 2 (Y)
C6M/2% C12D	87	1092	1.9 ± 0.1	59 ± 3 (Y)
Polycarbonate	150	1200	2.3	62 (Y)
Poly(DCPD) Telene 1100	145	1030	1.9	45

Many authors, including Nielsen [167], have utilized the kinetic theory of rubber elasticity [166] to calculate the molecular weight between cross-links, since above T_g , a cross-linked polymer behaves substantially like a rubber. Rubber elasticity relates the shear modulus, G , to the molecular weight between cross-links, M_c [165]. Figure 3.3-19 shows a comparison of molecular weights between cross-links calculated (i.e., theory) (solid line) and the measured shear modulus (●) for the C5M/C12D system. The results show that at low amounts of the cross-linker, the molecular weight between cross-links is less than theory predicts, while at high amounts of the cross-linker, the theory underestimates the molecular weight between cross-links. This has been attributed to physical entanglements and a proportion of the difunctional units being connected to the network at only one end.

Table 3.3-1 shows measured mechanical properties for the cross-linked materials and compares them with bis-phenol-A-polycarbonate and poly(DCPD) (Telene).

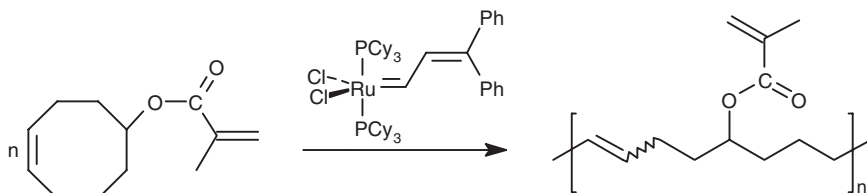
The room temperature moduli and ultimate bending strength of the cross-linked materials are, in general, higher than the equivalent thermosetting materials. Of particular interest are the high values for yield strength and toughness, which are comparable to known “high toughness” materials such as polycarbonates.

3.3.7.2

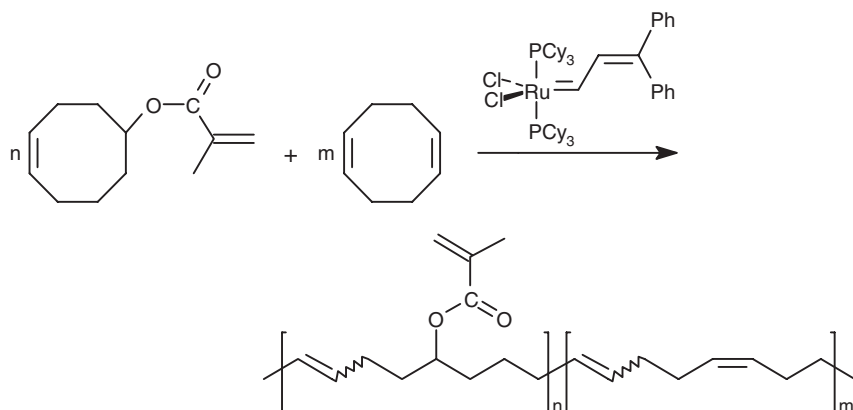
Cross-Linked Systems via Homopolymerization of Monomers with Cross-Linkable Side Chains

Cross-linkable polymers have found wide demand in the areas of interpenetrating polymer networks [168], nonlinear optical materials [169], macro- and micro-lithography [170], and formation of more thermally and chemically resistant materials [47]. The most versatile cross-linkable side chain is the methacrylate group, which polymerizes both thermally and photochemically in the presence of free-radical initiators and photosensitizers, respectively. The methacrylate group has found many applications in the UV curing of photoresists [171], coatings, and printing inks [172, 173]. Due to sensitivity of many metathesis catalysts to functional groups, the use of ROMP in the formation of these cross-linkable polymers has been limited. The high functional group tolerance of the $\text{Ru}(\text{=CHCH=CPh}_2)(\text{Cl})_2(\text{PPh}_3)_2$ initiator has prompted an investigation of the use of ROMP in the formation of cross-linkable polymers. In this study, 5-methacryloyl-1-cyclooctene was synthesized and polymerized by ruthenium vinylidene bistricyclohexanesphosphines, resulting in an alternating terpolymer of butadiene, polyethylene, and poly(vinyl methacrylate) with cross-linkable side chains spaced on average every eight carbons (Scheme 3.3-28). In addition, this monomer was copolymerized with COD, the homopolymer of which is polybutadiene, at varying feed ratios to systematically vary the number of methacrylate groups per chain (Scheme 3.3-29) [174, 175]. Cross-linking of these polymers was carried out both thermally and photochemically. Reaction of this multi-functionalized methacrylate polymer with MMA under free-radical polymerization conditions has led to the formation of AB cross-linked systems of PMMA.

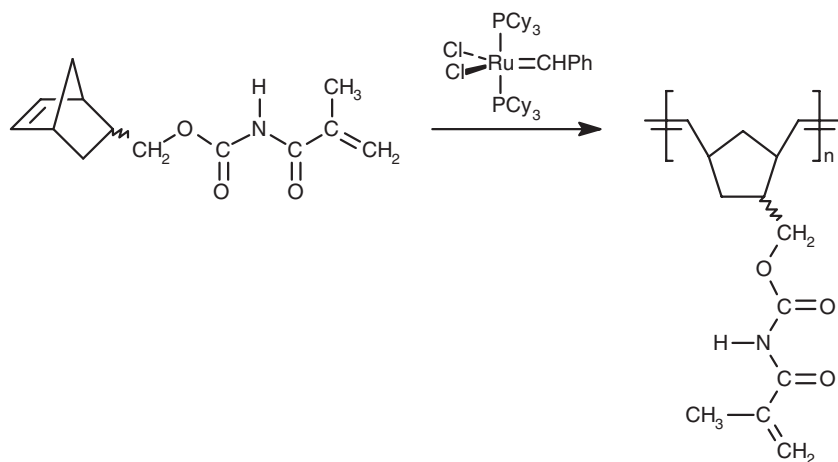
In a similar approach, a new functional monomer, 5-(methyl methacryloyl isocyanate)bicyclo[2.2.1]hept-2-ene, was metathesized using $\text{RuCl}_2(\text{=CHPh})(\text{PCy}_3)_2$ as the catalyst (Scheme 3.3-30). The incorporation of the resulting polymer into poly(methyl methacrylate) produced cross-linked materials that also had higher thermal stability and solvent resistance than pure PMMA [176].



Scheme 3.3-28

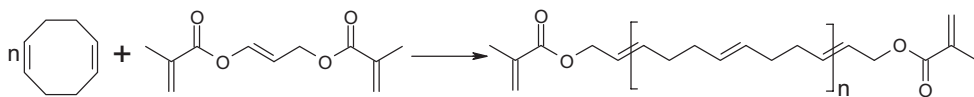


Scheme 3.3-29

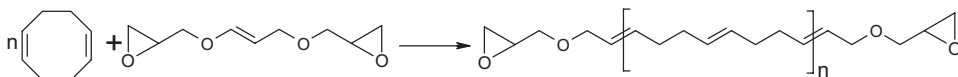


Scheme 3.3-30

The bis(methacrylate)- and bis (epoxide)-functionalized chain-transfer agents (CTAs) were successfully employed in the ROMP of COD for the preparation of cross-linkable telechelic poly(butylenes)s bearing either methacrylate or epoxide end groups (Schemes 3.3-31 and 3.3-32) [175]. The molecular weight of these telechelic poly(butylenes)s could be controlled by varying the initial $[COD]/[CTA]$ ratio. Thermal, photochemical, and acid-catalyzed cross-linking of the bis-



Scheme 3.3-31



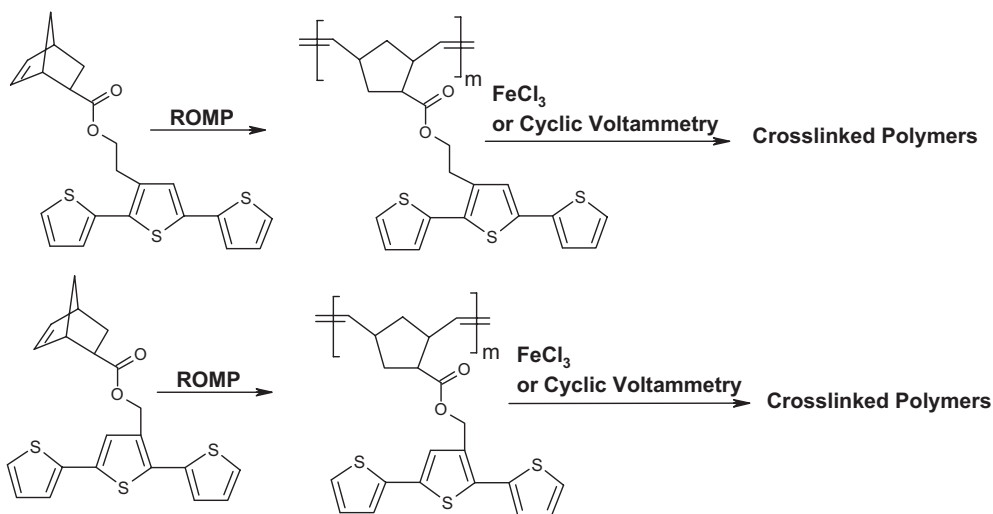
Scheme 3.3-32

functionalized telechelic poly(butylenes)s was also demonstrated. In contrast to the previously published approach for the preparation of cross-linkable polymers by ROMP of COD and 5-methacrylate-1-cyclooctene [174], this methodology allows the control of the polymer molecular weight between cross-links and should be more applicable to the preparation of cross-linkable polymers with varied backbone structures.

3.3.7.3

Cross-Linked Material via Combination of ROMP and Oxidative Polymerization

Polymers obtained from the oxidative polymerization of thiophenes, bithiophenes, and terthiophenes have been intensely studied because of the highly conjugated nature of the resulting materials. The synthesis and polymerization of norbornenyl-substituted thiophenes and terthiophene have been reported [177]. All monomers readily undergo ROMP using the ruthenium catalyst $\text{Ru}(\text{=CHR})(\text{Cl})_2(\text{PCy}_3)_2$. The polymeric materials obtained were cross-linked by oxidative or electrochemical polymerizations, Scheme 3.3-33. The control cross-linking of the ROMP polymers gave materials with conductivities that are within the range of conductivities associated with other poly(thiophenes).



Scheme 3.3-33

References

- 1 K. J. IVIN, *Olefin Metathesis*, Academic press, London, 1983.
- 2 J. KRESS, K. J. IVIN, V. AMIR-EBRAHIMI, P. WEBER, *Makromol. Chem.* **1990**, 191, 2237.
- 3 F. L. KLAFFETTER, R. H. GRUBBS, *J. Am. Chem. Soc.* **1988**, 110, 7807.
- 4 Z. WU, A. D. BENEDICTO, R. H. GRUBBS, *Macromolecules* **1993**, 26, 4975.
- 5 M. A. HILLMYER, A. D. BENEDICTO, S. B. NGUYEN, Z. WU, R. H. GRUBBS, *Macromol. Symp.* **1995**, 89, 411.
- 6 W. J. FEAST, V. C. GIBSON, K. J. IVIN, E. KHOSRAVI, A. M. KENWRIGHT, E. L. MARSHALL, J. P. MITCHELL, *Makromol. Chem.* **1992**, 193, 2103.
- 7 K. J. IVIN, J. KRESS, J. A. OSBORN, *J. Mol. Catal.* **1988**, 46, 351.
- 8 N. ZHANG, S. R. SCHRICKE, F. WUDL, M. PRATO, M. MAGGINI, G. SCORRANO, *Chem. Mater.* **1995**, 7, 441.
- 9 H. D. MAYNARD AND R. H. GRUBBS, *Macromolecules* **1999**, 32, 6917.
- 10 O. NUYKEN, S. PASK, *Telechelic Polymers*. In *Encyclopedia of Polymer Science and Technology*, J. I. KROSCSWITZ, Ed., Wiley-Interscience, New York, **1989**, vol. 16, pp521.
- 11 E. J. GOETHALS, *Telechelic Polymers: Synthesis and Applications*, CRC Press, Boca Raton, FL, **1989**.
- 12 C. HEPBURN, *Polyurethane Elastomers*, Elsevier Applied Science, New York, **1992**.
- 13 M. ZACHARIANSIEWICZ, *Urethane Technol.* **1986**, March, 32.
- 14 P. W. RYAN, *J. Elastoplast.* **1971**, 3, 57.
- 15 J. C. MARMO, K. B. WAGENER, *Macromolecules* **1993**, 26, 2137.
- 16 M. A. HILLMYER, R. H. GRUBBS, *Macromolecules* **1993**, 26, 872.
- 17 P. W. RYAN, J. Q. VERDOL, U.S. Patent 3 796 762, **1974**.
- 18 K. L. SELIMAN, U.S. Patent 2 877 212, **1959**.
- 19 C. FRASER, M. A. HILLMYER, E. GUTIERREZ, AND R. H. GRUBBS, *Macromolecules* **1995**, 28, 7256.
- 20 E. RUOSLAHTI, M. D. PIERSCHBACHER, *Science* **1987**, 238, 491.
- 21 M. D. PIERSCHBACHER, J. W. POLAREK, W. S. CRAIG, J. F. TSCHOP, N. J. SIPES, J. R. J. HARPER, *Cell. Biochem.* **1994**, 56, 150.
- 22 E. RUOSLAHTI, *Adv. Cancer Res.* **1999**, 1.
- 23 H. KOMAZAWA, I. SAIKI, Y. IGARASHI, I. AZUMA, M. KOJIMA, A. OIKASA, M. ONO, I. ITOH, *J. Bioact. Compat. Polym.* **1993**, 8, 258.
- 24 H. D. MAYNARD, S. Y. OKADA, AND R. H. GRUBBS, *Macromolecules* **2000**, 33, 6239.
- 25 X. LOU, C. DETREMBLEUR, P. LECOMTE, R. JEROME, *Polymer* accepted.
- 26 K. ZIEGLER, K. BAHR, *Chem. Ber.* **1928**, 61, 253.
- 27 M. SZWARC, V. M. BEYLEN, *Ionic Polymerization and Living Polymers*, Chapman and Hall, New York, **1993**.
- 28 O. W. WEBSTER, *Science* **1991**, 251, 887.
- 29 M. SZWARC, *Nature* **1956**, 178, 1168.
- 30 K. MATYJASZEWSKI, in *Cationic Polymerizations: Mechanisms, Synthesis, and Applications*, Marcell Dekker, Inc.: New York, **1996**.
- 31 M. MIYAMOTO, M. SAWAMOTO, T. HIGASHIMURA, *Macromolecules* **1984**, 17, 265.
- 32 O. W. WEBSTER, W. R. HERTLER, D. Y. SOGAH, W. B. FARNHAM, T. V. RAJAN-BABU, *J. Am. Chem. Soc.* **1983**, 105, 5706.
- 33 C. M. KILLIAN, D. J. TEMPEL, L. K. JOHNSON, M. K. BROOKHART, *J. Am. Chem. Soc.* **1996**, 118, 11664.
- 34 J. D. SCOLLARD, D. M. MCCONVILLE, *J. Am. Chem. Soc.* **1996**, 118, 10008.
- 35 R. BAUMANN, W. M. DAVIS, R. R. SCHROCK, *J. Am. Chem. Soc.* **1997**, 119, 3830.
- 36 T. OTSU, M. YOSHIDA, *Makromol. Chem. Rapid Commun.* **1982**, 3, 127.
- 37 M. K. GEORGES, R. P. N. VEREGIN, P. M. KAZMAIER, G. K. HAMER, *Macromolecules* **1993**, 26, 2987.
- 38 J. S. WANG, K. MATYJASZEWSKI, *J. Am. Chem. Soc.* **1995**, 117, 5614.
- 39 M. KATO, M. KAMIGAITO, M. SAWAMOTO, T. HIGASHIMURA, *Macromolecules* **1995**, 28, 1721.
- 40 V. PERCEC, B. BARBOIU, *Macromolecules* **1995**, 28, 7970.

- 41 J. KRESS, J. A. OSBORN, R. M. E. GREENE, K. J. IVIN, J. J. ROONEY, *J. Chem. Soc., Chem. Commun.* **1985**, 874.
- 42 R. M. E. GREENE, K. J. IVIN, J. J. ROONEY, J. KRESS, J. A. OSBORN, *Makromol. Chem.* **1988**, 189, 2797.
- 43 J. S. MURDZEK, R. R. SCHROCK, *Macromolecules* **1987**, 20, 2640.
- 44 W. J. FEAST, V. C. GIBSON, E. KHOSRAVI AND E. L. MARSHALL, *J. Chem. Soc., Chem. Commun.* **1994**, 9.
- 45 J. M. ZEIGLER, F. W. G. FEARSON, Eds. *Silicon-Based Polymer Science: A Comprehensive Resource*, American Chemical Society, Washington, DC, **1990**.
- 46 S. KANAOKA AND R. H. GRUBBS, *Macromolecules* **1995**, 28, 4707.
- 47 G. ODIAN, *Principles of Polymerization*, 3rd ed., Wiley, New York, **1991**.
- 48 Z. WU, D. R. WHEELER, R. H. GRUBBS, *J. Am. Chem. Soc.* **1992**, 114, 146.
- 49 Z. WU AND R. H. GRUBBS, *Macromolecules* **1994**, 27, 6700.
- 50 A. SPALTENSTEIN, G. M. WHITESIDES, *J. Am. Chem. Soc.* **1991**, 113, 686.
- 51 K. H. MORTELL, M. GINGRAS, L. L. KIESSLING, *J. Am. Chem. Soc.* **1994**, 116, 12053.
- 52 P. WANG, T. G. HILL, C. A. WARTCHOW, M. E. HUSTON, L. M. OEHLER, M. B. SMITH, M. D. BEDNARSKI, M. R. CALLSTROM, *J. Am. Chem. Soc.* **1992**, 114, 378.
- 53 K. NOMURA AND R. R. SCHROCK, *Macromolecules* **1996**, 29, 540.
- 54 A. V. VANNIKOV, A. D. GRISHINA, *Photochemistry of Polymer Donor-Acceptor Complexes*, Moscow, Nauka, **1984**.
- 55 D.-J. LIAW, C. H. TSAI, *J. Mol. Catal. A* **1999**, 147, 23.
- 56 D.-J. LIAW, P.-L. WU, C.-C. HUANG, *Macromol. Symp.* **2000**, 150, 313.
- 57 D.-J. LIAW, C.-C. HUANG, P.-L. WU, *Polymer* **2001**, 42, 9371.
- 58 D.-J. LIAW, P.-L. WU, *J. Mol. Catal. A: Chemical* **2000**, 160, 35.
- 59 H. FINKELMANN, U. KEICHLER AND G. REHAGE, *Mol. Cryst. Liq. Cryst.* **1983**, 94, 3453.
- 60 H. J. COLES, R. SIMON, In *Recent Advances in Liquid Crystalline Polymers*, L. L. CHAPOY, Ed., Elsevier Applied Science, New York, **1985**, Chapter 22.
- 61 H. FINKELMANN, H. RINGSDORF AND J. H. WENDROFF, *Makromol. Chem.* **1978**, 179, 273.
- 62 H. FINKELMANN, M. HAPP, M. PORTUGALL AND H. RINGSDORF, *Makromol. Chem.* **1978**, 179, 2541.
- 63 V. PERCEC AND C. PUGH, In *Side Chain Liquid Crystal Polymers*, C. B. McARDLE, Ed., Chapman and Hall, New York, **1989**, p30.
- 64 Z. KOMIYA, C. PUGH AND R. R. SCHROCK, *Macromolecules* **1992**, 25, 3609.
- 65 Z. KOMIYA, C. PUGH AND R. R. SCHROCK, *Macromolecules* **1992**, 25, 6586.
- 66 C. PUGH AND R. R. SCHROCK, *Macromolecules* **1992**, 25, 6593.
- 67 Z. KOMIYA AND R. R. SCHROCK, *Macromolecules* **1993**, 26, 1387.
- 68 Z. KOMIYA AND R. R. SCHROCK, *Macromolecules* **1993**, 26, 1393.
- 69 M. UNGERANK, B. WINKLER, E. EDER, AND F. STELZER, *Macromol. Chem. Phys.* **1995**, 196, 3623.
- 70 B. WINKLER, M. UNGERANK AND F. STELZER, *Macromol. Chem. Phys.* **1996**, 197, 2343.
- 71 M. WECK, B. MOHR, B. R. MAUGHON AND R. H. GRUBBS, *Macromolecules* **1997**, 30, 6430.
- 72 B. R. MAUGHON, M. WECK, B. MOHR AND R. H. GRUBBS, *Macromolecules* **1997**, 30, 257.
- 73 C. C. CUMMINS, M. D. BEACHY, R. R. SCHROCK, M. G. VALE, V. SANKARAN AND R. E. COHEN, *Chem. Mater.* **1991**, 3, 1153.
- 74 V. SANKARAN, R. E. COHEN, C. C. CUMMINS AND R. R. SCHROCK, *Macromolecules* **1991**, 24, 6664.
- 75 V. SANKARAN, C. C. CUMMINS, R. R. SCHROCK, R. E. COHEN AND R. J. SILBY, *J. Am. Chem. Soc.* **1990**, 112, 6858.
- 76 C. C. CUMMINS, R. R. SCHROCK, R. E. COHEN, *Chem. Mater.* **1992**, 4, 27.
- 77 Y. NG CHEONG CHAN AND R. R. SCHROCK, *Chem. Mater.* **1993**, 5, 566.
- 78 Y. NG CHEONG CHAN, G. S. W. CRAIG, R. R. SCHROCK AND R. E. COHEN, *Chem. Mater.* **1992**, 4, 885.

- 79 Y. NG CHEONG CHAN, R. R. SCHROCK AND R. E. COHEN, *Chem. Mater.* **1992**, 4, 24.
- 80 D. E. FOGG, L. H. RADZIŁOWSKI, R. BLANSKI, R. R. SCHROCK, AND E. L. THOMAS, *Macromolecules* **1997**, 30, 417.
- 81 J. M. NOTESTEIN, L. W. LEE, AND R. A. REGISTER, *Macromolecules* **2002**, 35, 1985.
- 82 P. DOUNIS, W. J. FEAST, *Polymer* **1996**, 37, 2547.
- 83 R. P. QUIRK, J. KUANG, *Polym. Int.* **1994**, 33, 181.
- 84 S. T. TRZASKA, L. W. LEE, R. A. REGISTER, *Macromolecules* **2000**, 33, 9215.
- 85 W. RISSE AND R. H. GRUBBS, *J. Mol. Catal.* **1991**, 65, 211.
- 86 W. RISSE AND R. H. GRUBBS, *Macromolecules* **1989**, 22, 4462.
- 87 A. E. WOODWARD, *Atlas of Polymer Morphology*, Hanser Publishers, Munich, **1988**.
- 88 S. POSHYACHINDA, H. G. M. EDWARDS, A. F. JOHNSON, *Polymer* **1991**, 32, 334.
- 89 G. W. COATES, R. M. WAYMOUTH, *Science* **1995**, 267, 217.
- 90 J. BROEDERS, W. J. FEAST, V. C. GIBSON, E. KHOSRAVI, *J. Chem. Soc. Chem. Commun.* **1996**, 343.
- 91 G. C. BAZAN, M. L. RENAK AND B. J. SUN, *Macromolecules* **1966**, 29, 1085.
- 92 J. H. BURROUGHS, D. D. C. BRADLEY, A. R. BROWN, R. N. MARKS, R. H. FRIEND, P. L. BURN AND A. B. HOLMES, *Nature* **1990**, 347, 539.
- 93 G. R. DAVIES, H. V. A. HUBBARD, I. M. WARD, E. L. MARSHALL, V. C. GIBSON, E. KHOSRAVI AND W. J. FEAST, *Polymer* **1995**, 36, 235.
- 94 R. R. SCHROCK, *Acc. Chem. Res.* **1990**, 23, 158.
- 95 R. R. SCHROCK, *Pure Appl. Chem.* **1994**, 66, 1447.
- 96 Y.-J. MIAO AND G. C. BAZAN, *J. Am. Chem. Soc.* **1994**, 116, 9379.
- 97 Y.-J. MIAO AND G. C. BAZAN, *Macromolecules* **1994**, 27, 1063.
- 98 M. A. HILLMYER, A. D. BENEDICTO, S. T. NGUYEN, Z. WU, AND R. H. GRUBBS, *Macromol. Symp.* **1995**, 89, 411.
- 99 B. M. NOVAK, W. RISSE AND R. H. GRUBBS, *Adv. Polym. Sci.* **1992**, 102, 47.
- 100 I. TRITTO, M. C. SACCHI AND R. H. GRUBBS, *J. Mol. Catal.* **1993**, 82, 103.
- 101 W. RISSE AND R. H. GRUBBS, *Macromolecules* **1989**, 22, 1558.
- 102 W. RISSE AND R. H. GRUBBS, *J. Mol. Catal.* **1991**, 65, 211.
- 103 M. KARO, M. KAMIGAITO, M. SAWAMOTO, T. HIGASHIMURA, *Macromolecules* **1995**, 28, 1721.
- 104 J.-S. WANG, K. MATYJASZEWSKI, *J. Am. Chem. Soc.* **1995**, 117, 5614.
- 105 T. E. PATTEN, J. XIA, T. ABERNATHY, K. MATYJASZEWSKI, *Science* **1996**, 272, 866.
- 106 S. COCA, H.-J. PAIK, AND K. MATYJASZEWSKI, *Macromolecules* **1997**, 30, 6513.
- 107 E. J. GOETHALS, *Telechelic Polymers: Synthesis and Applications*, CRC Press, Boca Raton, FL, **1989**.
- 108 C. W. BIELAWSKI, T. MORITA, AND R. H. GRUBBS, *Macromolecules* **2000**, 33, 678.
- 109 A. DEMONCEAU, F. SIMAL, S. DELFOSSE AND A. F. NOEL, *ROMP and related chemistry*, eds. E. KHOSRAVI AND T. SZYMANSK-BUZAR, NATO ASI Series, Kluwer Academic Publishers, **2002**.
- 110 A. NOSHAY, J. E. MCGRATH, *Block Copolymers*, Academic Press, New York, **1977**.
- 111 M. WECK, P. SCHWAB AND R. H. GRUBBS, *Macromolecules* **1996**, 29, 1789.
- 112 W. J. FEAST, V. C. GIBSON, A. F. JOHNSON, E. KHOSRAVI AND M. A. MOHSIN, *Polymer* **1994**, 35, 3542.
- 113 W. J. FEAST, V. C. GIBSON, A. F. JOHNSON, E. KHOSRAVI AND M. A. MOHSIN, *J. Mol. Catal. A: Chemical* **1997**, 115, 37.
- 114 A. C. M. RIZMI, E. KHOSRAVI, W. J. FEAST, M. A. MOHSIN AND A. F. JOHNSON, *Polymer* **1998**, 39, 6605.
- 115 A. DEMONCEAU, A. F. NOELS, E. SAIVE, AND A. J. HUBERT, *J. Mol. Catal.* **1992**, 76, 123.
- 116 A. DEMONCEAU, A. W. STUMPF, E. SAIVE, AND A. F. NOELS, *Macromolecules* **1997**, 30, 3127.
- 117 P. LECOMTE, D. MECERREYES, P. DUBOIS, A. DEMONCEAU, A. F. NOELS, AND R. JÉRÔME, *Polym. Bull.* **1998**, 40, 631–638.

- 118 D. MECERREYES, D. DAHAN, P. LECOMTE, P. DUBOIS, A. DEMONCEAU, A. F. NOELS, AND R. JÉRÔME, *J. Polym. Sci. Part A: Polym. Chem.* **1999**, 37, 2447.
- 119 F. SIMAL, A. DEMONCEAU, AND A. F. NOELS, *Angew. Chem. Int. Ed.* **1999**, 38, 538.
- 120 F. SIMAL, A. DEMONCEAU, AND A. F. NOELS, *Tetrahedron Lett.* **1999**, 40, 5689.
- 121 F. SIMAL, L. DELAUDE, D. JAN, A. DEMONCEAU, AND A. F. NOELS, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1999**, 40(2), 336.
- 122 C. W. ALLEN, *Chem Rev.* **1991**, 91, 119.
- 123 J. M. NELSON, A. P. PRIMROSE, T. J. HARTLE, H. R. ALLCOCK, *Macromolecules* **1998**, 31, 947.
- 124 H. R. ALLCOCK, C. R. DE DENUS, R. PRANGE, AND W. R. LAREDO, *Macromolecules* **2001**, 34, 2757.
- 125 K. NOMURA, S. TAKAHASHI, AND Y. IMANISHI, *Macromolecules* **2001**, 34, 4712.
- 126 S. BREUNIG, V. HÉROGUEZ, Y. GNANOU, M. FONTANILLE, *Macromol. Symp.* **1995**, 95, 151.
- 127 V. HÉROGUEZ, Y. GNANOU, M. FONTANILLE, *Macromol. Rapid. Comm.* **1996**, 17, 137.
- 128 V. HÉROGUEZ, S. BREUNIG, Y. GNANOU, M. FONTANILLE, *Macromolecules* **1996**, 29, 4459.
- 129 Y. GNANOU, V. HÉROGUEZ, M. FONTANILLE, *Macromolecules* **1997**, 30, 4792.
- 130 D. GRANDE, J. L. SIX, V. HÉROGUEZ, Y. GNANOU, M. FONTANILLE, *Macromol. Symp.* **1998**, 128, 21.
- 131 V. HÉROGUEZ, J. L. SIX, Y. GNANOU, M. FONTANILLE, *Macromol. Chem. Phys.* **1998**, 199.
- 132 D. GRANDE, J. L. SIX, S. BREUNIG, V. HÉROGUEZ, Y. GNANOU, M. FONTANILLE, *Polymers for Advanced Technologies* **1998**, 9, 601.
- 133 V. HÉROGUEZ, E. AMEDRO, D. GRANDE, M. FONTANILLE, Y. GNANOU, *Macromolecules* **2000**, 33, 7241.
- 134 T. LESNE, V. HÉROGUEZ, Y. GNANOU, R. DUPLESSIX, *Colloid Polym. Sci.* **2001**, 279, 190.
- 135 V. HEROGUEZ, Y. GNANOU, ROMP and related chemistry, edits. E. KHOSRAVI AND T. SZYMANSK-BUZAR, NATO ASI Series, Kluwer Academic Publishers, **2002**.
- 136 G. C. BAZAN, R. R. SCHROCK, *Macromolecules* **1991**, 24, 817.
- 137 R. S. SAUNDERS, R. E. COHEN, S. J. WONG, R. R. SCHROCK, *Macromolecules* **1992**, 25, 2055.
- 138 E. DRENT, P. H. M. BUDZELAAR, *Chem. Rev.* **1996**, 96, 663.
- 139 B. AL SAMAK, A. G. CARVILL, J. G. HAMILTON, J. J. ROONEY, J. M. THOMPSON, *Chem. Commun.* **1997**, 2057.
- 140 B. AL SAMAK, V. AMIR-EBRAHIMI, D. G. CORRY, J. G. HAMILTON, S. RIGBY, J. J. ROONEY, J. M. THOMPSON, *J. Mol. Cat.* **2000**, 160, 13.
- 141 J. G. HAMILTON, K. J. IVIN, J. J. ROONEY, L. C. WARING, *J. Chem. Soc., Chem. Commun.* **1983**, 159.
- 142 T. L. CHOI, I. M. RUTHENBERG, R. H. GRUBBS, *Angew. Chemie*, accepted.
- 143 L. X. WANG, B. T. HUANG, *J. Polym. Sci., Part B: Poly. Phys.* **1991**, 29, 1447.
- 144 P. AALTONEN, J. SEPPALA, L. MATILAINEN, M. LESKELA, *Macromolecules* **1994**, 27, 3136.
- 145 M. BROOKHARDT, F. C. RIS, J. M. DESIMONE, C. J. BARBORAK, *J. Am. Chem. Soc.* **1992**, 114, 5894.
- 146 A. SEN, *Adv. Polym. Sci.* **1986**, 73/74, 125.
- 147 E. DRENT, J. A. M. VAN BROEKHOVEN, M. J. DOYLE, *J. Organomet. Chem.* **1991**, 417, 235.
- 148 Z. WU AND R. H. GRUBBS, *Macromolecules* **1995**, 28, 3502.
- 149 M. F. ILKER AND E. B. COUGHLIN, *Macromolecules* **2002**, 35, 54.
- 150 R. J. MINCHAK, US Patent 4,426,502, issued 17/01/1984.
- 151 L. MATEJKA, C. HOUTMAN AND C. W. MACOSKO, *J. Appl. Polym. Sci.* **1985**, 30, 2787.
- 152 R. H. GRUBBS, L. K. JOHNSON, S. T. NGUYEN, US Patent No. 5,312,940, issued 5/17/1994.
- 153 R. H. GRUBBS, L. K. JOHNSON, S. T. NGUYEN, US Patent No. 5,342,909, issued 8/30/1994.
- 154 R. H. GRUBBS, S. T. NGUYEN, L. K. JOHNSON, US Patent No. 5,710,298, issued 1/20/1998.

- 155 R. H. GRUBBS, C. S. WOODSON, JR., US Patent No. 5,728,785, issued 3/17/1998.
- 156 C. S. WOODSON, JR., R. H. GRUBBS, US Patent No. 5,939,504, issued 8/17/1999.
- 157 D. S. BRESLOW, *Chemtech*. **1990**, 540.
- 158 J. A. JOHNSON, M. F. FARONA, *Polym. Bull.* **1991**, 25, 625–627.
- 159 H. NG, I. MANAS-ZLOCZOWER, M. SHMORHUN, *Polym. Eng. Sci.* **1994**, 34, 921–928.
- 160 A. BELL, *Polym. Preprints* **1994**, 35, 694–695.
- 161 E. KHOSRAVI AND A. A. AL-HAJAJI, *Eur. Polym. J.* **1998**, 34, 153.
- 162 E. KHOSRAVI AND A. A. AL-HAJAJI, *Polymer* **1998**, 39, 5619.
- 163 E. KHOSRAVI, W. J. FEAST, A. A. AL-HAJAJI, T. LEEJARKPAI, *Mol. Catal. A: Chemical* **2000**, 160, 1.
- 164 T. LEEJARKPAI, PhD Thesis, University of Durham, UK, **2000**.
- 165 P. J. HINE, T. LEEJARKPAI, E. KHOSRAVI, R. A. DUCKETT, AND W. J. FEAST, *Polymer* **2001**, 42, 9413.
- 166 L. R. G. TRELOAR, *The Physics of Rubber Elasticity*, Oxford, London, UK, **1958**.
- 167 L. E. NIELSEN, *Journal of Macromolecular Science – Rev. Macromol. Chem.* **1969**, C3(1), 69.
- 168 B. DAS, D. CHAKRABORTY, A. K. HAJRA, S. SINHA, *J. Appl. Polym. Sci.* **1994**, 53, 1491.
- 169 B. K. MANDAL, J. KUMAR, J. HUANG, S. TRIPATHY, *Makromol. Chem. Rapid Commun.* **1991**, 12, 63.
- 170 A. REISER, *Photoreactive Polymers*, Wiley and Sons, Inc, New York, **1988**.
- 171 A. C. SCHWENTHALER, U.S. Pat. 3,418,295, Dec. 24, **1968**.
- 172 V. D. MCGINNIS, *Ultraviolet Light Induced Reactions in Polymers*, American Chemical Society Symposium Series 25, American Chemical Society, Washington, DC, **1976**.
- 173 B. B. KINE, R. W. NOVAK, Eds. *Acrylic and Metahcrylic Ester Polymers*, *Encyclopedia of Polymer Science and Engineering*, Wiley and Sons, Inc, New York **1985**, Vol. 1.
- 174 B. R. MAUGHON AND R. H. GRUBBS, *Macromolecules* **1996**, 29, 5765.
- 175 B. R. MAUGHON, T. MORITA, C. W. BIELAWSKI, AND R. H. GRUBBS, *Macromolecules* **2000**, 33, 1929.
- 176 D.-J. LIAW, J.-S. TSAI, AND P.-L. WU, *Macromolecules* **2000**, 33, 6925.
- 177 K. J. WASON, P. S. WOLFE, S. T. NGUYEN, J. ZHU, AND C. A. MIRKIN, *Macromolecules* **2000**, 33, 4628.

3.4

Conjugated Polymers

W. James Feast

3.4.1

Introduction

In this chapter we are concerned with metathesis routes to the conjugated polymers that have become a topic of intense theoretical and experimental interest during the last 30 years or so and that, at the time of writing, appear to be in the process of making an entry into serious manufacturing enterprises. Before getting into the meat of the topic, it seems desirable to set the context by describing how and why conjugated polymers became worthy of our attention. Historically, probably the first public demonstration of the useful application of an organic conjugated polymer occurred in the northeastern England on 3 February 1879, when Joseph Swan demonstrated electric lighting to the Newcastle-upon-Tyne Literary and Philosophical Institute [1]. Swan was an entrepreneurial Victorian chemist with very broad interests, and he was encouraged by a successful engineer, William Armstrong, to find a way of using the electricity produced by Armstrong's turbines to provide domestic lighting. At that time several people were pursuing the same objective, and we can assume that the approach to the solution of this problem was largely empirical. Swan's solution involved treating cotton fibers with sulfuric acid and then pyrolyzing them to produce the graphitic carbon filaments that became incandescent when enclosed in an evacuated glass bulb and subjected to an electrical current. At about the same time in the U.S., Thomas Edison, quite independently, achieved very similar results, initially via pyrolysis of fibers obtained from specific types of fibrillated bamboo. After the inevitable tensions concerning priority and intellectual property rights, the Edison and Swan United Electric Light Company was founded, which sold light bulbs based on incandescent graphitic carbon filaments profitably until the brighter and more robust tungsten filament lamps displaced them. Some of these carbon filament light bulbs still exist; they give a yellow-toned light that is softer than most modern bulbs.

After this interlude there was a long pause before conjugated organic polymers reappeared as objects of interest in academic research and, eventually, in industrial exploitation. The renaissance of interest developed from the speculations of theo-

reticians concerning the likely properties of well-defined conjugated organic polymers; the close interplay among theory, physics, organic synthesis, and technology that characterized the origins of this topic remains a characteristic feature of the field up to the present day. The area of structurally defined organic polymers attracted theoreticians because the paradigm for the field, polyacetylene, has an apparently simple structure that might reasonably be expected to be amenable to theoretical analysis and predictive modeling. In the 1930s the introduction by Huckel [2] of a theory dealing with the structure and properties of unsaturated systems stimulated Lennard-Jones [3] to compute the properties of polyacetylene and led to the prediction that this simple organic polymer would have a π electronic structure consisting of a half-filled continuous band somewhat reminiscent of the view of the electronic structure postulated for electrically conductive metals; by analogy, it was proposed that this simple organic polymer might well display metallic electrical conductivity. About 20 years later, Longuet-Higgins and Salem [4] carried out fresh calculations and concluded that there would be a Peierls distortion in polyacetylene resulting in alternating carbon-carbon bond lengths rather than the complete delocalization and equivalent carbon-carbon bond lengths implied by Lennard-Jones. As a consequence, they predicted that the full π bonding and empty π anti-bonding levels would not form a continuous half-filled band but would exist as two bands separated by a band gap. They further predicted that polyacetylene would probably be a fairly poor semiconductor or an insulator, depending on the size of the gap, a prediction that was subsequently validated experimentally for the case of the carefully handled pristine materials.

Natta and coworkers [5] reported the first synthesis of polyacetylene, namely, the obvious direct route via chain-growth polymerization of acetylene initiated by Ziegler-Natta catalysts such as $(C_2H_5)_3Al/Ti(OC_4H_9)_4$ in a hydrocarbon solvent such as heptane. By bubbling acetylene through the catalyst solution at room temperature and atmospheric pressure, they obtained polyacetylene as a red powder that was identified as predominantly the *trans* isomer (Figure 3.4-1b) on the basis

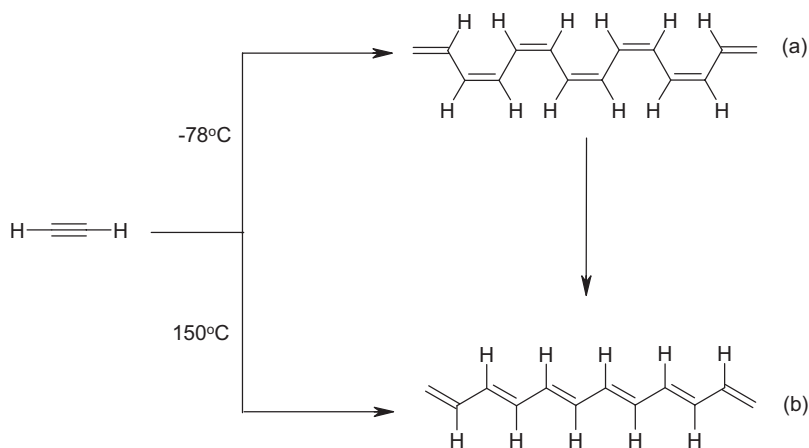


Fig. 3.4-1. Polymerization of acetylene and isomerization of polyacetylene.

of X-ray diffraction analysis. The material was insoluble, infusible, and very sensitive to atmospheric oxidation and therefore was regarded as an unattractive polymer. Natta does not appear to have examined its electrical properties. Subsequent work showed that polymerization of acetylene at low temperature gave predominantly the *cis* isomer (Figure 3.4-1a). The *cis* isomer can exist only at low temperatures. As samples of polyacetylene prepared at low temperature are allowed to warm up to room temperature, even in the solid state where conformational reordering might be expected to be inhibited, the polymer isomerizes (Figure 3.4-1a,b) to a predominantly *trans* structure. This change is accompanied by an increase in the free spin density (revealed by ESR measurements) and electrical conductivity.

Berets and Smith, working for Cyanamid in the U.S., appear to have been the first to examine the electrical properties of polyacetylene. They took the unpromising intractable powder produced in Natta's experiment and compressed it at 100,000 psi to obtain the material as a silvery disc that displayed poor semiconductor properties. The conductivity of this compressed disc was increased on exposure to volatile oxidants, such as iodine, and reduced on exposure to ammonia [6]. An explosion of interest in polyacetylene and related conjugated organic polymers followed Ikeda and Shirakawa's report of the polymerization of acetylene using the same reagents that Natta had described but manipulating the experimental protocol so as to allow polymerization to occur at the interface between gaseous acetylene and the surface of a concentrated solution of $(C_2H_5)_3Al/Ti(OC_4H_9)_4$ in heptane, rather than in solution. This modification allowed the production of polyacetylene as a film that could be washed, sliced, and manipulated for experimental investigations. The films were generally obtained as low-density porous mats of denser semi-crystalline fibrils, which allowed easy access for solutions of oxidizing and reducing reagents to the bulk of the material. It was quickly established that polyacetylene underwent massive redox modification upon exposure to either oxidizing or reducing agents [8], and it is now generally accepted that the conductivity of this superficially simple polymer can be varied from values characteristic of a good insulator to those characteristic of a good metallic conductor. Values as low as $10^{-14} \text{ S cm}^{-1}$ have been obtained for clean *cis*-polyacetylene prepared at low temperature by the Shirakawa route, and values of 10^5 S cm^{-1} or higher have been reported for iodine-oxidized stretch-aligned films [9]. A material whose electrical conductivity can be varied over 19 to 20 orders of magnitude is clearly very remarkable and worthy of study. The most common forms of polyacetylene have predominantly *trans* geometry at the double bonds, have structural defects in the form of sp^3 carbons and probably cross links, and are electrically neutral, but have free spins (radicals located at mid-gap where the sense of the conjugation in the polyene chain is reversed) and are poor semiconductors. When subjected to redox chemistry (reduction or oxidation, chemical or electrochemical), they undergo increases in conductivity of several orders of magnitude and large structural changes to accommodate the counter ions intercalated into the fibrillar segments to balance the charges created on the polyene chains. Pristine polyacetylene also displays a large third-order, nonlinear optical effect. This

remarkable combination of properties in one superficially simple material attracted enormous interest among chemists, physicists, theoreticians, and electrical and electronics engineers. There was an explosion of activity during the last three decades of the last century; polyacetylene was investigated, *inter alia*, as a potential storage battery electrode, as the semiconductor component of electronic devices such as FETs, and as the active component of nonlinear optical devices. Although all the anticipated phenomena and device structures were successfully demonstrated, at present none of these investigations has led to the commercialization of devices based on polyacetylene. Despite these disappointments, there can be no doubt that this material acted as the paradigm for the whole field of conducting polymers and stimulated the search for better materials. The contributions of Shirakawa, MacDiarmid, and Heeger to stimulating this field of endeavor were recognized by the award of the Nobel Prize for Chemistry for 2000.

Despite its very interesting combination of properties, polyacetylene was, and generally still is, regarded as an unattractive material from a technical point of view because it is unstable in the presence of oxygen and light, is insoluble, and cannot be melt processed. Taken individually, none of these disadvantages is technologically insurmountable. Atmospheric instability can be overcome by encapsulation, and powder processing does not require solubility or melting, but in combination they have both inhibited the exploitation of this remarkable material and stimulated the search for alternative conjugated polymer materials that combine interesting electro-optical properties with enhanced stability and ease of processing. The subject is one of intense activity, and there are many hundreds of publications on all aspects of the subject in primary research journals, reviews, and books [10]. In addition, the area has spawned its own specialist journal, *Synthetic Metals*. Here we shall focus on the possibility of obtaining conjugated polymers using ROMP-based methodologies.

3.4.2

Strategies for Applying ROMP in the Synthesis of Conjugated Polymers

The extended π conjugation required for the development of the attractive electro-optic properties associated with conjugated polymers leads to a requirement for extended planarity in the molecular skeleton. This, in turn, directs us to the less appealing features of conjugated polymers, namely, their inherent insolubility and infusibility, which inhibit conventional polymer processing. A variety of strategies have been adopted to overcome these problems, including:

- Attaching substituents to enhance solubility and increase processability. Such substituents may be placed either pendant to the main chain or at the chain ends. The introduction of main-chain substituents has to be carefully designed and executed in order to avoid steric inhibition of conjugation by twisting the molecular skeleton out of planarity. Solubilizing substituents at chain ends may be introduced as components of block copolymers, and in this case the trade-off

- among enhanced processability, reduced conjugated polymer content, and phase segregation effects has to be sorted out empirically.
- Formation of the required conjugated polymer *in situ* directly from monomer. This approach has the virtue of simplicity if it can be made to work.
 - Design and synthesis of a processable precursor of the desired polymer. Such precursors have to be converted to the desired material *in situ* after processing without release of noxious side products or other damaging side effects.

In practice all these approaches have been developed for particular systems. In the specific case of ROMP methodologies, the usual choice between step- or chain-growth assembly mechanisms has to be considered independent of whether a direct or precursor route is being adopted. We will first consider direct routes from monomer to conjugated polymer via chain-growth processes, followed by direct step-growth processes, and finally we will review precursor routes.

3.4.3

Direct Routes from Monomer to Conjugated Polymer Via Chain-Growth Processes

An attractive feature of ring-opening metathesis polymerization, as far as making conjugated polymers is concerned, is that the π unsaturation of the monomer is retained in the product polymer. Carrying this observation to its logical conclusion, we might expect that ROMP of conjugated cyclic polyenes, if achievable, would be an appropriate route to polyacetylene and other conjugated polymers. If we consider the even-membered conjugated cyclic polyenes as potential ROMP monomers, we can assume that cyclobutadiene will be too reactive for consideration as a monomer and benzene will be too stable. Consequently, cyclooctatetraene and its substituted derivatives appear to be the first and, since higher-membered, conjugated cyclic polyenes are not readily available, only suitable monomers for polyacetylene synthesis via this route. Several groups have examined this reaction, which is summarized in Figure 3.4-2.

Using the “classical” initiator system $\text{WCl}_6/\text{Al}(\text{C}_2\text{H}_5)_2\text{Cl}$ in toluene, Korshak et al. were the first to demonstrate the feasibility of this approach (Figure 3.4-2, $\text{R} = \text{H}$). They obtained polyacetylene as a black powder, but in only 6% yield [11]. Subsequently, the same group showed that catalyst and protocol modification could improve the yield to 40% [12]. This was achieved by using the catalyst



Fig. 3.4-2. Ring-opening metathesis polymerization of cyclooctatetraene and substituted cyclooctatetraenes.

$W(\text{OCH}(\text{CH}_2\text{Cl})_2)_n \text{Cl}_{6-n}/\text{Al}(\text{C}_2\text{H}_5)_2\text{Cl}$ as the initiator and condensing the cyclo-octatetraene directly onto a layer of solid catalyst. These authors reported the formation of oligomeric side products, including the cyclic polyenes $(\text{CH}=\text{CH})_n$ where $n = 5-8$, which were identified by mass spectrometry, and these observations demonstrated the existence of backbiting reactions in competition with polymerization in this system. In this early work it was also reported that the *cis* double-bond content depended on the Al:W ratio; at an Al:W ratio of 1, a blue/black film with a *cis* vinylene content of $>80\%$ was reported, whereas at an Al:W ratio of 2, the film had a golden hue and $<40\%$ *cis* vinylene content.

Using the Schrock [13], $W(=\text{CHC}(\text{CH}_3)_3)(=\text{NAr})(\text{OC}(\text{CH}_3)(\text{CF}_3)_2)_2$, and Osborn [14], $W(=\text{CHC}(\text{CH}_3)_3)(\text{OCH}_2\text{C}(\text{CH}_3)_2\text{Br}_2.\text{GaBr}_3$, well-defined catalysts, the Grubbs' group was able to demonstrate much better control of this reaction [15]. Dissolving these catalysts in neat cyclooctatetraene resulted in the formation of high-quality lustrous films of polyacetylene within a few seconds. These films had a silvery hue and smooth surfaces, and this synthesis protocol represents an example of the well-controlled generation of a conjugated polymer *in situ*. The monomer cyclooctatetraene has all *cis* double bonds and the initial ROMP product would be expected to contain predominantly *cis* vinylene units; however, it is known that the thermodynamically stable configuration of polyacetylene is the *trans* transoid form (see Figure 3.4-3), and it is this form that is of interest with respect to semiconducting behavior. Solid-state ^{13}C nuclear magnetic resonance is the analytical probe of choice for monitoring the isomerization dynamics and structure of solid polyacetylene. The exact shifts observed depend on *cis/trans* vinylene geometry and the nature of the nearest neighbor vinylenes so that the evolution of chain microstructure can be followed. In the pristine as made material, two peaks are observed. The more intense peak, corresponding to *cis* vinylene units in all *cis* sequences, occurs at 126.4 ppm, with a weaker signal for the *trans* vinylenes in *cis* sequences occurring at 132.2 ppm. Upon thermal isomerization, the spectrum changes and the original signals decay and are eventually replaced by a dominant peak at 135.9 ppm, which is attributed to carbons in *trans* transoid sequences. The peak has a small upfield shoulder attributed to residual *cis* units between *trans* vinylenes. This development represented a significant improvement in the processability of polyacetylene, since in the liquid stage of the neat polymerization, the solution could be painted out onto substrates. Although films of the homopolymer are somewhat brittle, they can be coated onto a rigid substrate

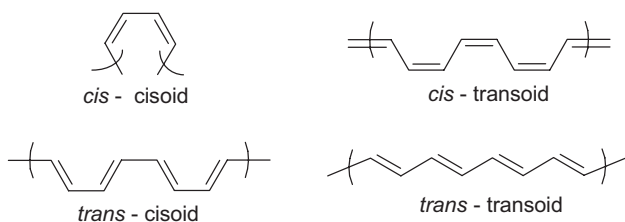


Fig. 3.4-3. Isomeric microstructures for polyacetylene.

and examined for both semiconducting (pristine material) and conducting (after exposure to volatile redox reagents) properties. It turned out that this new form of polyacetylene displayed structural features and physical properties similar to those of conventional Shirakawa polyacetylene (density, X-ray diffraction spacing, I_2 -oxidized conductivity) but has a smoother surface and a lower intrinsic conductivity ($<10^{-8}$ cf. 10^{-5} S cm $^{-1}$), suggesting a somewhat higher purity; of course, the experimental procedures required for its preparation, in particular the elimination of the requirement to work with gaseous acetylene, give it an advantage as the method of choice for preparation of this type of material. Copolymers of cyclooctatetraene with 1,5-cyclooctadiene and norbornene are readily obtained by this method, and the distribution of polyene block lengths can be controlled through the monomer feed ratio, allowing control of processability, film color, and conductivity. For example, films of poly(cyclooctadiene) are colorless, but copolymers with 20% cyclooctatetraene comonomer are orange, with 40% are red, with 80% are red-black, and with 100% are silver [16].

In an extensive program of work [15–26], the Grubbs' group has made a very thorough study of the scope of this methodology for the preparation of polymeric polyenes. They varied the catalyst system used, the range of monomers (cyclooctatetraene and substituted cyclooctatetraenes) and comonomers (mono- and polycyclic olefins), and the reaction conditions. A wide range of novel materials were produced, characterized, and studied, and some of the conclusions of this large body of work are reviewed below.

As mentioned above, the homopolymer produced from cyclooctatetraene could be obtained as smooth lustrous films but was rather brittle; however, the introduction of substituents allowed circumvention of this problem. It is well established that the polymerization of mono- and disubstituted acetylenes leads to polyenes in which adjacent double bonds are formally conjugated in the sense that there are alternating double and single carbon-carbon bonds along the polymer backbone but are effectively not conjugated because there is no π overlap between adjacent double bonds. Thus, poly(*t*-butylacetylene) and poly(hexafluoro-2-butyne) are known polyenes, and both are white due to steric interactions between neighboring substituents twisting the polyene backbone so that successive π bonds are mutually perpendicular. When a monosubstituted cyclooctatetraene is polymerized to give a substituted polyacetylene, the substituents can, in principle, occur once on every eight carbons of the backbone; however, when neat monomer is used, some backbiting reactions occur, resulting in 7–16% elimination of C_6H_5R . No benzene was detected, from which it can be concluded that no ROMP at the substituted double bonds occurs and that the substituents occur on every fourth or fifth double bond in the chain, since ROMP can occur at any of the other three double bonds in the monomer and some of the substituents in the feed are eliminated as C_6H_5R . Consequently, the 1,2- and 1,3-placement of substituents normally required for significant steric interaction is vanishingly small. It was found that for the process depicted in Figure 3.4-2, the initially formed substituted polyenes were generally soluble in solvents such as THF or CH_2Cl_2 but tended to become less soluble as the nascent *cis* vinylene sequences isomerized to *trans* on prolonged standing at

room temperature or warming, which is consistent with expectations based on decreasing disorder in the solute. When R (Figure 3.4-2) is methyl, the product polymer is brittle and completely insoluble, like polyacetylene, but films of polymers carrying butyl or larger *N*-alkyl substituents are flexible and very slightly soluble. The as-made polymers are red-brown in solution but turn blue on prolonged standing at room temperature, consistent with the postulated isomerization process. These polymers can be oxidized by iodine into the metallic conductivity regime. Branched chain or aromatic substituents do not improve the solubility greatly. Thus, when R is neopentyl or phenyl, the as-made polymers are completely soluble but become effectively insoluble as the *trans* vinylene content increases. When R is *t*-butyl, the polymer is completely soluble; unfortunately, putting this bulky substituent close to the polyene chain results in steric inhibition of backbone planarity, and this material is yellow, indicating a limited undistorted conjugation length. Consistent with this observation, this polymer remains an insulator even after oxidation with iodine.

However, with the appropriate choice of substituent, fully soluble and highly conjugated forms of substituted polyacetylene could be obtained. Indeed, when R is trimethylsilyl, this desirable objective was realized [17]. The processable polyenes prepared by this methodology have been investigated as components of device structures including Schottky barrier devices [19, 23] and solar cells [18, 23], with interesting consequences in both cases. Diodes formed at the semiconductor/metal interface when the “metal” component is an organic polymer and the semiconductor is n-silicon behave more ideally than contacts with conventional metals, inasmuch as changes in the electrical properties of the conducting organic polymer brought about by redox chemistry exert a large and predictable effect on the diode characteristics [19]. This is probably attributable to the milder processing conditions required to deposit the conjugated polymer as compared to the energetic vacuum sputtering required for the conventional metals. In the case of solar cells produced by coating thin transparent films of trimethylsilyl-substituted polyacetylene onto n-type silicon and then oxidizing the conjugated polymer layer with iodine vapor to form surface-barrier cells, it was reported that the photo voltages were at the theoretical limit and were much greater than those obtained from devices based on thin films of conventional metals vacuum-deposited onto n-type silicon [18]. Again, this improvement may well be attributable to the milder processing conditions involved in the polymer device construction.

Space limitations preclude discussing all aspects of the program of work summarized by Figure 3.4-2, but the effect of making the R group chiral merits a brief mention. Soluble chiral polyacetylenes have been made and characterized [21]. The π to π^* transition associated with the conjugated backbone of such polymers shows a pronounced CD effect, showing that in these polymers the backbone chain must be dissymmetric or in a dissymmetric environment. Thus, the presence of a chiral substituent on the backbone results in twisting the chain predominantly in one sense rather than just electronically perturbing the chromophore. This observation indicates that the polyene chain in solution is conformationally mobile, but whether this solution chirality can be transferred to solid films and what the tech-

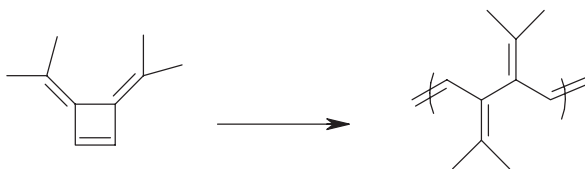


Fig. 3.4-4. ROMP of 3,4-diisopropylidenecyclobutene to give a cross-conjugated polymer.

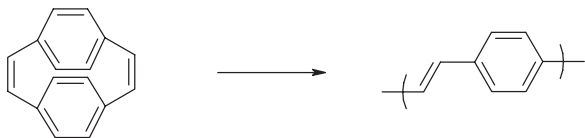


Fig. 3.4-5. ROMP of [2.2]paracyclophane-1,9-diene to give poly(paraphenylene vinylene).

nological implications might be are not clear at present. The bulk of the work on synthesis of highly conjugated derivatives of polyacetylene via ROMP of mono-substituted cyclooctatetraene has been reviewed and the relationship between structure and properties collated [24]; however, at the time of this writing, this topic remains active, and the continuous development of catalyst capability and activity suggests that the story is far from finished. For example, while the catalyst $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ does not polymerize cyclooctatetraene, the more active system $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)(\text{IMesH}_2)$ does and gives films of polyacetylene with conductivities comparable to those first produced by Shirakawa [26].

While it is not strictly an example of a direct ROMP route to a conjugated polymer, the synthesis outlined in Figure 3.4-4 merits comment here. 3,4-Diisopropylidenecyclobutane is polymerized by ROMP using an initiator system that can be regarded as a source of $\text{Cp}_2\text{Ti}=\text{CH}_2$ [27]. The product polymer has a backbone structure made up of sp^2 carbons but is really cross-conjugated rather than conjugated. Nevertheless, although films of the pristine polymer are insulators, oxidation with iodine vapor gives conductivities up to $10^{-3} \text{ S cm}^{-1}$.

The poly(arylene vinylene)s have attracted considerable interest since Burroughes et al. described their use as the electroluminescent layer in polymer-based, light-emitting diodes [28]. From the point of view of a ROMP route to such materials, [2.2]paracyclophane-1,9-diene is the obvious monomer. Thorn-Csányi and coworkers have shown that ROMP of this monomer (see Figure 3.4-5) gives poly(paraphenylene vinylene) (PPV) as an insoluble yellow fluorescent powder; soluble copolymers can be obtained with cyclopentene, cyclooctene, and cycloocta-1,5-diene [29–31]. In the UV-vis spectra of the copolymers with cyclooctene, distinct absorption peaks are resolved that can be assigned to sequences of one, two, and three paraphenylene vinylene repeat units. This shows that the polymer formation is not a straightforward chain-growth ROMP reaction, since the presence of the units with one and three paraphenylene vinylene repeat units can arise only from secondary metathesis at the vinylenes. Bazan and coworkers have also contributed to the understanding of this reaction, showing that

[2.2]paracyclophane-1-ene (the monomer in Figure 3.4-5 with one double bond saturated) can be polymerized in toluene solution using the Schrock initiator $\text{Mo}(=\text{CHC}(\text{CH}_3)_2\text{Ph})(=\text{NAr})(\text{OC}(\text{CH}_3)(\text{CF}_3)_2)_2$ to give a soluble polymer that has 98% *cis* vinylenes. If these double bonds are isomerized to the *trans* geometry by irradiation or warming with a trace of iodine, the polymer rapidly becomes insoluble [32], once again emphasizing the processing problems inherent in this field of activity. To circumvent the solubility, this group attached a solubilizing group, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$, at one of the saturated carbons in [2.2]paracyclophane-1-ene. The polymer from this monomer remains soluble even when all the vinylenes have *trans* geometry, the silyl group can be replaced by hydroxyl under tetrabutylammonium fluoride catalysis, and the resulting polymer can be dehydrated thermally or under acid catalysis to give PPV [33]. There are several fairly obvious continuations to this approach, but major advances have been inhibited, generally by the solubility problems referred to above. For example, ROMP of ferrocenophanes (ferrocenes with the cyclopentadienyls bridged by a vinylenes) initially gave only oligomers, but higher-molecular-weight products could be obtained by introducing substituents and by copolymerization [34].

3.4.4

Direct Routes from Monomer to Conjugated Polymer Via Step-Growth Processes

Following on from the synthesis of PPV via ROMP of [2.2]paracyclophane-1,9-diene (see above and Figure 3.4-5), the most successful approach to the synthesis of conjugated polymers using a step-growth metathesis approach is summarized in Figure 3.4-6. This approach is discussed in detail in the chapter by Wagener on ADMET (Chapter 3.9) and therefore is described here only briefly for the sake of completeness. The subject has been reviewed recently by Stelzer [35] and by E. Thorn-Csányi [36].

The process depicted in Figure 3.4-6 is inhibited by the insolubility of the product when R is hydrogen or a small alkyl group; however, when R is butyl or larger, soluble oligomers are obtained that have all-*trans* vinylenes and a surprisingly narrow molecular weight distribution and are easily processed by conventional solution techniques. Figure 3.4-7 illustrates the range of monomers introduced by the Stelzer group. Both groups have favored use of the Schrock initiator $\text{Mo}(=\text{CHC}(\text{CH}_3)_2\text{Ph})(=\text{NAr})(\text{OC}(\text{CH}_3)(\text{CF}_3)_2)_2$ after investigating a range of catalysts. Surprisingly, this reaction does not appear to be readily driven to high-molecular-weight products, but nevertheless it gives clean, defect-free materials

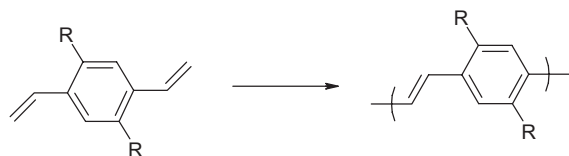


Fig. 3.4-6. Step-growth approach to PPVs using the ADMET approach.

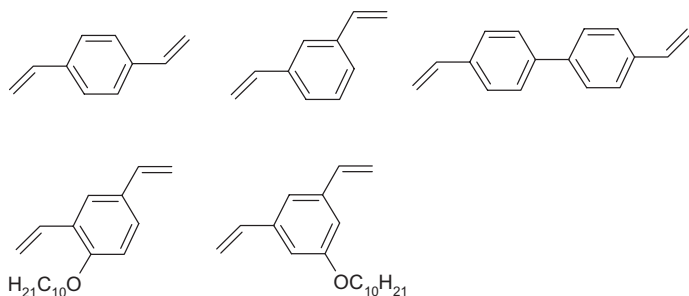


Fig. 3.4-7. Monomers used in PPV syntheses.

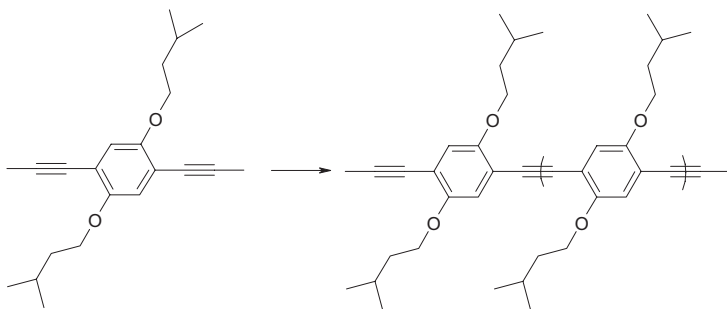


Fig. 3.4-8. Step-growth approach to “molecular wires” using metathesis polymerization of diacetylenes.

in which the photoluminescence efficiency of the products often exceeds 50%. Because the value quoted for PPV, the standard workhorse for the field, is generally about 27%, materials prepared in this way appear to be quite attractive.

Poly(phenylene ethynylene)s may be prepared via step-growth metathesis polymerization of the diacetylene monomer as shown in Figure 3.4-8. Alkyne metathesis and alkyne metathesis polymerization are dealt with in detail elsewhere in this handbook and therefore are covered here only briefly for the sake of completeness. These rigid, rod-conjugated polymers have attracted interest, and Weiss and coworkers and others have reported a considerable body of work in this area. Key factors that emerge from this promising approach to the construction of electronic devices based on molecules are that catalyst and monomer selection is crucial if progress is to be made. Thus, Weiss has shown that although Schrock carbyne complexes of the type $\text{Np}_3\text{WCC}(\text{CH}_3)_3$, $((\text{CH}_3)_3\text{CO})_3\text{WCC}(\text{CH}_3)_3$, and $\text{Cl}_3(\text{dme})\text{WCC}(\text{CH}_3)_3$ are effective catalysts for the chain-growth metathesis polymerization of a variety of substituted monoacetylenes, only $\text{Cl}_3(\text{dme})\text{WCC}(\text{CH}_3)_3$ was effective for the step-growth synthesis shown in Figure 3.4-8 and for related polymerizations of diacetylenes. This group also developed a method for end capping their rigid rod polymers using the monoalkyne 1-(N,N-dimethylcarbamothioic)-4-(1-propynyl)benzene. After reaction with oligomers derived from 1,4-di(1-propynyl)-2,5-dihexylbenzene, the end group can be removed to leave a thiol at

each chain end, which is postulated as the anchor of the molecular wire to a gold electrode. The purification of individual thiol-ended poly(phenylene ethynylene) oligomers and their manipulation into the appropriate configuration on a substrate present formidable challenges, but this is an interesting approach to a challenging problem. Weiss has reviewed the synthesis work recently [37], and this remains an active area.

3.4.5

Indirect Routes to Conjugated Polymer Via Processable Precursor Polymers

The organic chemist's normal approach to the synthesis of molecules or materials that are delicate, sensitive to the environment, or intractable is to mask the susceptible part of the molecule with a protecting group. Protecting groups have to be easily introduced, stable to all the conditions from which they should protect the molecule, and easily removed when their task is done. The development of an armory of protecting groups for all purposes was one of the major achievements of synthetic organic chemistry through the last century and remains an important activity. As we have explained above, conjugated polymers are often either environmentally sensitive and/or insoluble, infusible, and generally unattractively intractable materials. We have reviewed various ways of circumventing these disadvantages in the previous sections, and we conclude this chapter by discussing the advantages and problems associated with producing conjugated polymers from processable precursors. This approach has been of interest in the author's group for some years [38–54]. Therefore, we will consider some of that early work first, since it illustrates the advantages and problems associated with this approach. The synthesis, which is generally known as the Durham precursor route to polyacetylene, was first established experimentally by Edwards [38, 39], but in the earliest years of the project, an interactive group of chemists (Durham), physicists (Cambridge), and materials chemists (Sussex) was set up under the guidance and funding of BP Research Centre (Sunbury), which proved valuable in developing the interdisciplinary approach required in this area of activity. The contributions of the scientists from the four centers involved in this study are acknowledged by reference in the following discussion.

The synthetic route is summarized in Figure 3.4-9. The monomer, a tricyclic triene, is prepared in good yield via the Diels-Alder reaction of an acetylene (in Figure 3.4-9 hexafluorobut-2-yne) with bicyclo[4.2.0]octa-2,4,7-triene, the valence isomer of cyclooctatetraene. This work predated access to the well-defined ROMP initiators, and the polymerization was initiated with the "classical" very active and indiscriminating system WCl_6/Ph_4Sn . ROMP occurs exclusively at the cyclobutene double bond to give a soluble precursor that can be characterized by conventional solution-phase methods before being spin- or dip-coated onto an appropriate substrate and converted *in situ* to polyacetylene. The elimination of the aromatic leaving group (in Figure 3.4-9, 1,2-bis(trifluoromethyl)benzene) is a symmetry-allowed ground-state process [42] that occurs slowly in solution or solid state

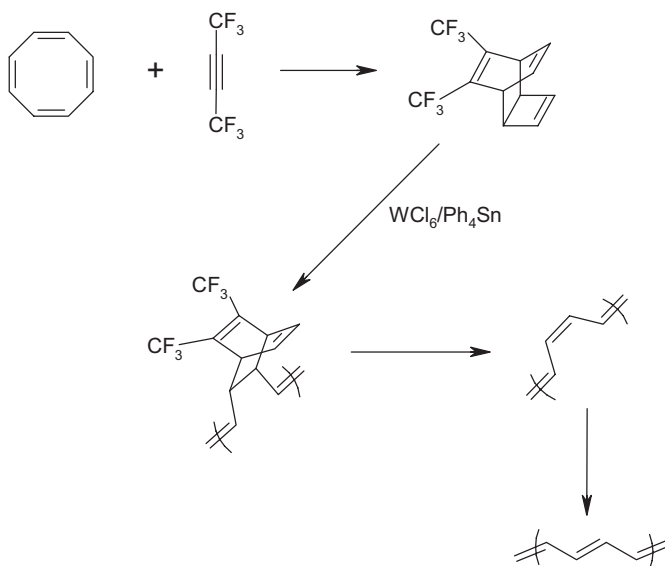


Fig. 3.4-9. The Durham precursor route to polyacetylene.

at room temperature. Consequently, samples had to be stored and precursor polymer characterization measurements (spectroscopy and size exclusion chromatography) carried out at low temperature in a cold room. Genuine high-molecular-weight precursor polymers are obtained with weight average molecular weights in the 400,000 to 1,000,000 range, corresponding to 3000–7500 double bonds in the final polyacetylene chain, assuming no fragmentation during conversion. The process of conversion of the precursor polymer to polyacetylene is complex, and the nature of the polyacetylene produced is controlled by the conversion protocol adopted. Precursor films cast from solution are fully dense; the polymer is atactic, with a statistical distribution of *cis* and *trans* vinylenes; the first elimination step generates a *cis* vinylenes in the chain and an aromatic unit; and the *cis* vinylenes isomerize to the *trans* geometry with concomitant solid-state reorganization of the material. The aromatic unit migrates through the reorganizing film and is lost by evaporation; at the same time, the volume and mass of the film decreases dramatically. The occurrence of all these processes overlap in time and space. The polyacetylene produced by this route is different from that made by the Shirakawa or Grubbs routes discussed in earlier sections. The material is formed as a fully dense, continuous, pinhole-free film, with a density of $1.05 \text{ g} \cdot \text{cm}^{-3}$, compared to $0.3\text{--}0.4 \text{ g} \cdot \text{cm}^{-3}$ for the mats of fibers obtained by the Shirakawa route. The material also differs in the crystal structure and the electrical and optical properties. The structure varies from essentially amorphous, for the usual as-made polymer, to highly crystalline, in materials that are stretch aligned prior to or during conversion. The electrical and optical properties reflect these differences in a consistent way. Thus, stretch-aligned films display optical and electrical anisotropy and sig-

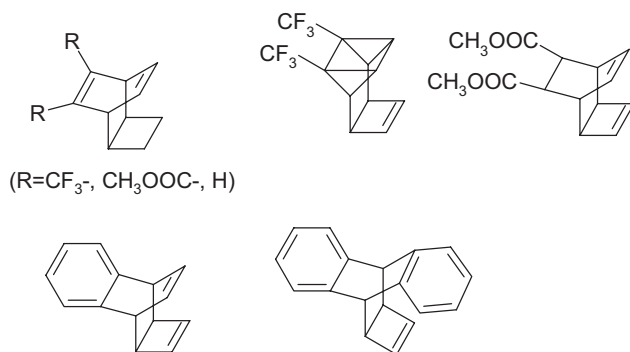


Fig. 3.4-10. Monomers investigated for use in the Durham precursor route to polyacetylene.

nificantly higher carrier mobilities than the isotropic amorphous material. The fully converted pristine film has an electrical conductivity of $3 \times 10^{-8} \text{ ohm} \cdot \text{cm}^{-1}$, comparable to samples of the Grubbs material but 2 or 3 orders of magnitude lower than typical Shirakawa material, and films undergo redox modification into conductivity regimes similar to those reported by Grubbs and Shirakawa. The preparation, conversion, and properties of the unoriented material have been collated and discussed in detail [45]. Having established a precursor route to polyacetylene that provided interestingly different forms of the material, some effort was put into designing better monomers; some examples are shown in Figure 3.4-10. In the event all these monomers were polymerized and copolymerized by us and by others [55–58], but the system outlined in Figure 3.4-9 remains the most convenient to use. Thus, the monomer derived from hexafluoro-2-butyne can be readily obtained in good yield by a one-step reaction, it undergoes polymerization with a variety of ROMP initiators, and the eliminated aromatic unit migrates through and evaporates from the film without problem. The only inconvenience is the room temperature thermal instability. The monomer produced by photoisomerization of the original tricyclic triene monomer (middle top line in Figure 3.4-10) readily undergoes ROMP to give a kinetically stable precursor polymer that can be converted to polyacetylene, provided that only thin films are contemplated and appropriate precautions are adopted [41, 48]. The repeat unit of the precursor in this case contains a combination of 2-, 3-, and 4-membered carbon rings fused together; the conversion to polyacetylene is symmetry forbidden in the ground state, which accounts for the kinetic stability of the precursor, but the stored strain energy is considerable, and conversion of anything other than very thin films results in explosions! The tricyclic diene shown in Figure 3.4-10 also undergoes ROMP readily. The resulting precursor would require elimination of a cyclohexa-1,3-diene derivative; while this is formally a ground-state symmetry-allowed process, it does not occur below the decomposition temperature of the polymer and no polyacetylene was obtained. The two monomers shown at the bottom of Figure 3.4-10 also undergo ROMP readily [39]; the precursors are soluble, form films, are thermally stable, and undergo conversion to polyacetylene by

elimination of naphthalene and anthracene, respectively. The enhanced thermal stability is presumably a reflection of the reduced gain in thermodynamic stability in the formation of a bi- or tricyclic aromatic as compared to a monocyclic aromatic during the conversion step; however, these materials are not, in our view, useful precursors to polyacetylene since the eliminated aromatics are difficult to remove from the product films, which are usually mechanically degraded by the process. Therefore, as is often the case, it appears that the first design was the best, and the effort put into trying to improve it was misspent, albeit interesting.

The precursor polymer shown in Figure 3.4-9 often exists in a form in which conversion to polyene has occurred to an extent that allows the polymer to remain soluble but is pale yellow to orange (pristine precursor maintained at low temperature is colorless). This does not affect the processability but does present another manipulation possibility, namely, photolithography and pattern construction in conjugated polymers. Thus, UV irradiation of partially converted (yellow/orange) thin films of precursor polymer through a photolithographic mask in the presence of air, followed by heating, results in the transfer of the mask image into the film as a relief image with a line resolution of 0.3 μm ; the photobleached parts of the precursor consist of a transparent fluorinated polymeric insulator with a thickness of about 70% of the original film, whereas the unirradiated parts convert to polyacetylene at about 30% of the thickness of the original film [47, 50].

The Friend group's [59, 60] preparation and characterization of Schottky-barrier diode, MIS diode, and MISFET structures using polyacetylene derived from the precursor route as the active semiconducting component of the device structure demonstrated the potential of what is now known as "plastic electronics." However, while the work was interesting and stimulating and allowed a thorough investigation of the materials' physics [60], the devices appeared to have little chance of exploitation since the carrier mobilities were too low to be of practical use. It was observed that stretch-aligned polyacetylene displayed generally superior properties [52] and, in particular, higher carrier mobilities; therefore, the question arose of how to generate aligned polyacetylene in a solvent cast and thermally converted polymer. A partial solution to this question is summarized in Figure 3.4-11, and the route adopted is crucially dependent on the availability of well-defined initiators, in this case the $\text{Mo}(=\text{CHC}(\text{CH}_3)_2\text{Ph})(=\text{NAr})(\text{OC}(\text{CH}_3)_3)_2$ developed by the Schrock group. The approach uses the route described above (Figure 3.4-9), but the well-defined initiator replacing the "classical" $\text{WCl}_6/\text{Ph}_4\text{Sn}$ system allows the well-defined living polymerization of the fluorinated tricyclic triene monomer. As a result, the living precursor is formed in a narrow polydispersity molecular weight controlled by the monomer-to-initiator ratio. The living polymer can be capped by addition of an aldehyde to give a precursor that is soluble and of well-defined molecular weight and carries a self-ordering unit at the chain ends [53, 54]. Spin-cast films of this precursor undergo spontaneous self-ordering during conversion to give thin films of polyacetylene displaying carrier mobilities several orders of magnitude higher than those found in the conventional amorphous polymer or in a placebo sample containing a tertiary butyl group at both chain ends. This approach had been used previously by Schrock for the preparation of

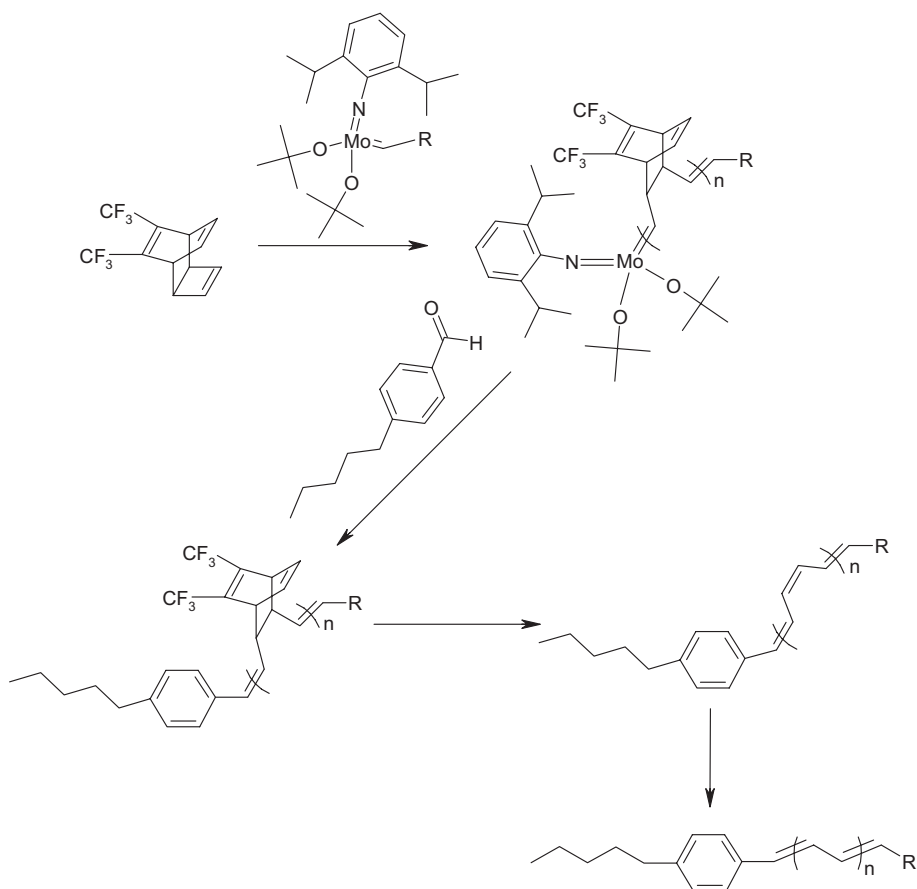


Fig. 3.4-11. Use of living ROMP methodology to make “self-organizing polyacetylene.”

polyene oligomers capped by *t*-butyl groups, which were individually isolated chromatographically in order to study the correlation of spectroscopic properties with chain length [58]. The Schrock group also demonstrated phase separation effects in a block copolymer of the Durham precursor and norbornene. In this case phase segregation led to a different sort of ordering of polyacetylene, namely, a distribution of microdots in a polynorbornene matrix, a phenomenon seen elsewhere [56].

In an effort to avoid the massive mass loss associated with the Durham route, Grubbs examined the ROMP of benzvalene and isomerization of the resulting polymer [61, 62]. The concept was proved but the strain energy per repeat unit in the precursor polymer means that it is prone to detonation; nevertheless, it can be converted to polyacetylene under mercury salt catalysis, although the iodine-induced conductivity is low and the ^{13}C NMR spectroscopic analysis indicates a significant sp^3 carbon content.

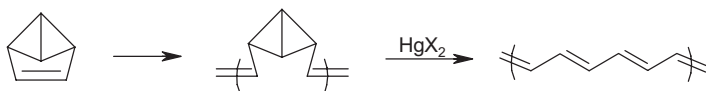


Fig. 3.4-12. The poly(benzvalene) precursor route to polyacetylene.

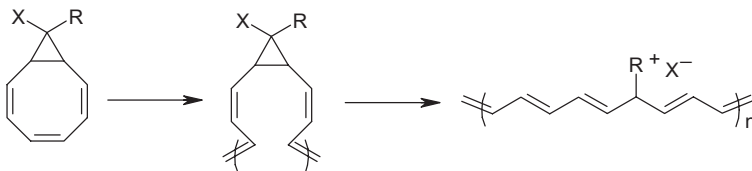


Fig. 3.4-13. A potential precursor route to p-type polyacetylene.

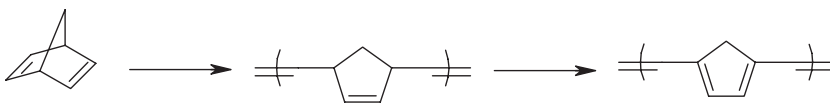


Fig. 3.4-14. Basis of precursor routes to conjugated polymers relying on dehydrogenation of a precursor.

The scheme outlined in Figure 3.4-13 has been investigated in the author's laboratory but not been made to work as of yet. The concept is to make a cationically modified conjugated polymer via isomerization of a precursor; in this respect, it is a relative of the idea giving rise to the scheme shown in Figure 3.4-12. While the idea looks feasible and should lead to a conjugated polymer with a cation on every ninth carbon, the range of initiators tried so far did not effect ROMP. This failure has been discussed before [63], but the observation of the polymerization of cyclooctatetraene by the latest generation of ruthenium-based Grubbs catalysts [26] suggests it might be worth trying again.

There are, of course, many potential syntheses that “look good on paper” but do not work in practice. In the remaining part of this chapter, we will consider examples of other precursor routes that work and some that do not work and attempt to explain the reasons why.

Figure 3.4-14 summarizes several pieces of work based on the concept of dehydrogenating a precursor polymer to give a conjugated polymer. This is an interesting concept that has met with mixed success in practice. In part, the problem lies in the chemistry selected for the process, the “strength” of the reagents, and the nature of the nascent product polymer. Ideally, a precursor polymer should undergo deprotection or conversion to product cleanly and in a unique sense. In the simplified generalized scheme shown in Figure 3.4-14, the precursor is required to undergo dehydrogenation (oxidation), and the products of reaction and surplus reagent should be immediately removed because the nascent conjugated segments are inherently likely to be as easily or even more easily oxidized than the pristine precursor. In this case, and in several cases that have been reported, the nascent conjugated segment is a chemically reactive cyclopentadiene unit, and the reactivity of this unit with itself and any reagent in the vicinity has to be

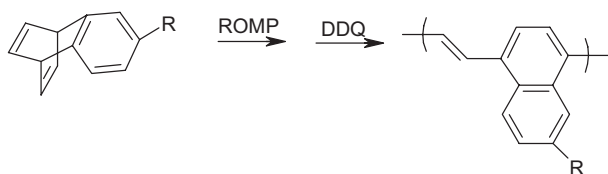


Fig. 3.4-15. A two-step precursor route to substituted poly(naphthylene vinylene)s.

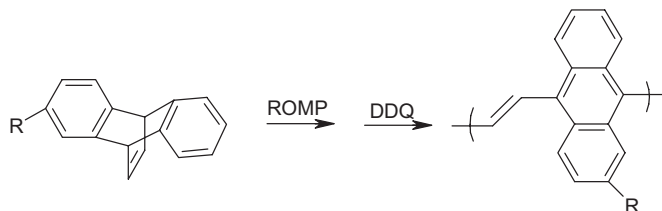


Fig. 3.4-16. A two-step precursor route to substituted poly(anthracenylene vinylene)s.

taken into account, as does the wholesale conformational reorganization consequent in going from a system with two vinylene units *syn* to each other on a 5-membered ring (the precursor) to an essentially planar, somewhat graphitic structure. With these considerations in mind it is perhaps surprising that this approach works at all, but in well-designed cases it has been very successful. Figures 3.4-15, 3.4-16, and 3.4-17 summarize dehydrogenating precursor systems that work [64–66]. The first example, Figure 3.4-15, involves the ROMP of hexyl- and undecyl-substituted benzobarrelenes [64, 65] using the molybdenum-carbene initiators. In line with expectation, the *cis/trans* ratio in the product polymer depended on the catalyst used and the reaction condition, but with the well-defined Schrock initiator $\text{Mo}(=\text{CHC}(\text{CH}_3)_2\text{Ph})(=\text{NAr})(\text{OC}(\text{CH}_3)(\text{CF}_3)_2)_2$, the reaction proceeds fairly slowly to give the expected precursor polymer in good yield, reasonable molecular weight ($M_w \sim 60,000$), and relatively broad polydispersity. The broad polydispersity is probably due to termination reactions and/or the relatively slow initiation relative to propagation. The precursor polymers were dehydrogenated using 2,3-dichloro-5,6-dicyanoquinone (DDQ) to give solution-processable, relatively stable substituted poly(naphthylene vinylene)s that were strongly fluorescent and that underwent oxidation with nitrosonium tetrafluoroborate to give films with conductivities of about $\sim 10 \text{ ohm cm}^{-1}$, which is 2 orders of magnitude higher than the unsubstituted analogue. The solid-state photoluminescence of these materials was relatively modest, $\sim 3\%$ for the homopolymers and $\sim 10\%$ for blends with polystyrene, possibly due to intermolecular quenching in these structurally regular and probably fairly well-ordered materials. Figure 3.4-16 summarizes the analogous route to poly(anthracenylene vinylene)s reported by Stelzer and coworkers [35]. They used the same initiator and experimental conditions as the Grubbs group but obtained a low-molecular-weight product with a mixture of *cis* and *trans* vinylenes rather than an all-*trans* system. The monomer in this case is more sterically hindered than that shown in Figure 3.4-15. The earlier monomer presented two equivalent double bonds to the growing polymer chain end, whereas

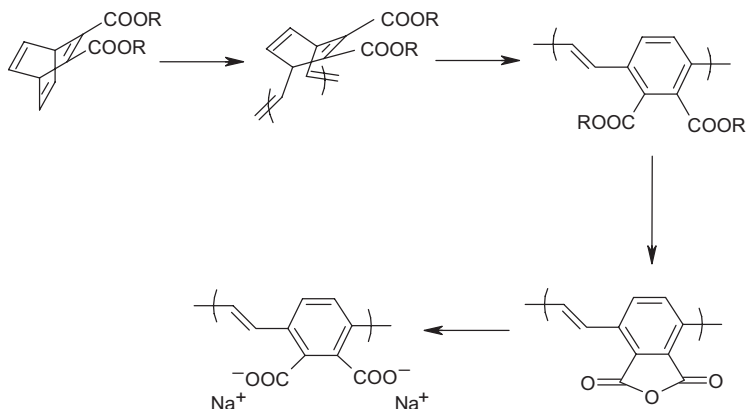


Fig. 3.4-17. Precursor routes to modified poly(phenylene vinylene)s.

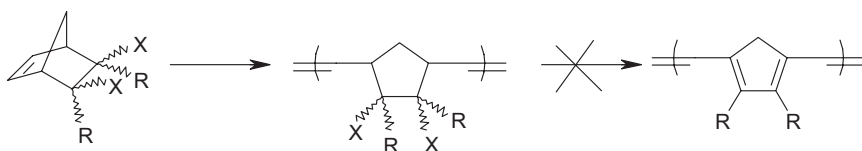


Fig. 3.4-18. Postulated routes to conjugated polymers via dehydrohalogenation of precursor polymers.

in this case only one hindered double bond is available. The precursor polymer was dehydrogenated with DDQ in an analogous manner, but these workers found it very difficult to remove the DDQH_2 from the poly(anthracenylene vinylene) product; presumably there was a strong interaction between the anthracene residues (relatively easily oxidized) and the DDQ or DDQH_2 . Whatever the reasons, these workers were unfortunate in their system, which serves to underline the validity of the pessimistic preamble to this section. Another successful system is outlined in Figure 3.4-17. In this work 2,3-dicarboxybicyclo[2.2.2]octa-2,5,7-trienes, substituted barralenes, were polymerized in benzene or methylene chloride using the same protocols and catalysts reported above. Addition of hexafluoro-*t*-butanol and THF to the polymerization mixture had a marked accelerating effect on the rate. The precursor polymers obtained were successfully dehydrogenated with DDQ to give ester-substituted derivatives of PPV. Hydrolysis of the esters allowed the synthesis of the anhydride and sodium carboxylate derivatives, thus giving rise to a water-soluble fluorescent PPV derivative. Interestingly, the partial dehydrogenation (80%) of the precursor polymer gave a significantly higher photoluminescence efficiency than did the completely converted material, again indicating the advantage, as far as photoluminescence is concerned, of having a disordered structure.

Figures 3.4-18 and 3.4-19 show two often tried but essentially unsuccessful “plausible paper chemistry” routes to conjugated polymers via a precursor made by ROMP. In Figure 3.4-18 the concept involves ROMP of a halogenated norbornene monomer made via Diels-Alder cycloaddition between a halogenated

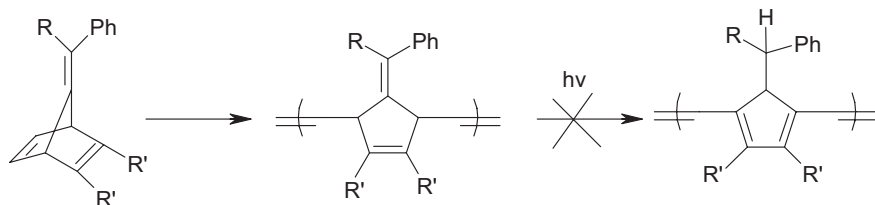


Fig. 3.4-19. Postulated route to conjugated polymers via photoisomerization of a precursor polymer.

olefin and cyclopentadiene, followed by dehydrohalogenation of the resulting precursor polymer. The hydrogen to be removed is tertiary and allylic and, for the 1,2-eliminations, requires that the four atoms involved are close to coplanar, which is expected to favor elimination. However, to the best of the author's knowledge, all the attempts to put this concept into practice have failed. The precursor polymers are readily obtained, and some have potentially interesting properties as pyro-, piezo- and electrostrictive materials, but all attempts to dehydrohalogenate them thermally or with various bases (from aqueous to non-nucleophilic-hindered bases) result in polymer degradation, and structurally well-defined conjugated polymers are not obtained (although it has been known for authors to claim conjugated polymer synthesis on the basis of an organic polymer going black on pyrolysis). Similar strictures apply to attempts to make polyacetylene by dehydrochlorination of PVC. The route probably fails because the polymer films cannot accommodate the conformational strain imposed and because the hydrogen halide eliminated in the first step is a very effective catalyst for degradation and isomerization of the nascent conjugated segments.

For the scheme outlined in Figure 3.4-19, the monomer was produced by cycloaddition of an acetylene to a substituted fulvene; this monomer underwent ROMP readily to give a soluble transparent "precursor" polymer that was expected to undergo a photochemically promoted 1,3-migration of the tertiary bis-allylic hydrogen atom, followed by a 1,2-hydrogen shift to give the conjugated polymer structure shown. Although plausible, the process did not work and the "precursor" polymer proved to be surprisingly photo-stable, remaining transparent after UV irradiation.

The final precursor routes to be presented here rely on enolization to generate the conjugated system. Figure 3.4-20 summarizes the work of Harper [67]. He took the Diels-Adler adduct of dichlorovinylene carbonate with cyclopentadiene and showed that it underwent ROMP with "classical" catalysts to give the chlorinated precursor polymer shown. The precursor is a soluble, film-forming material. Upon exposure of the surface of a film of this precursor to aqueous acid or base, the colorless transparent film is transformed into a lustrous "metallic" film. Based on the knowledge that the monomer under the same conditions is converted to norbornene-5,6-diketone, together with IR and UV-vis spectroscopic evidence, it was postulated that the lustrous film was a consequence of the formation of the conjugated polymer shown on the bottom right of Figure 3.4-20. However, this

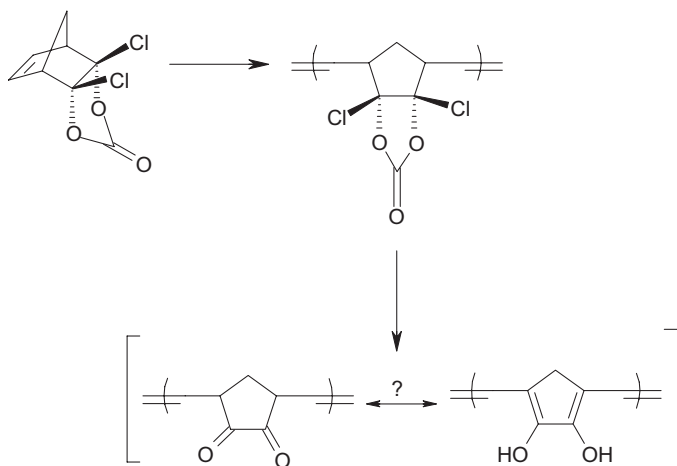


Fig. 3.4-20. Route to a conjugated polymer using enolization of a diketonic precursor.

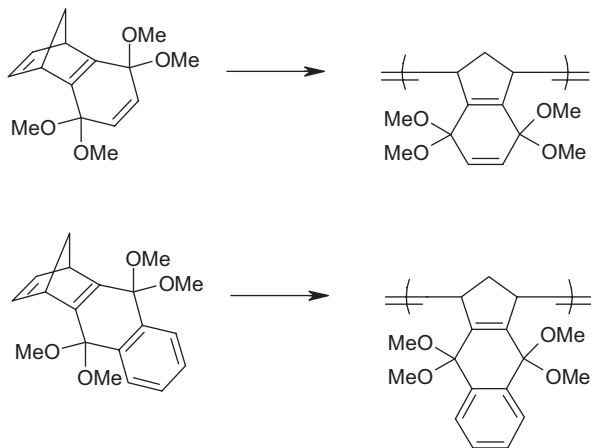


Fig. 3.4-21. ROMP synthesis of a precursor to a conjugated polymer to be formed via an enolization step.

investigation was not pursued further since the lustrous film was extraordinarily susceptible to oxidation by atmospheric oxygen and was very difficult to handle; indeed, it was suggested that it might make a reasonable glove box oxygen scavenger.

The final example in this section is related to the previous one; Figure 3.4-21 shows two monomers derived from quinones, both of which are readily polymerized under ROMP conditions. The polymers were investigated as solution-processable precursors to conjugated polymers, which were anticipated as likely to be insoluble. As shown in Figure 3.4-22, hydrolysis converted the precursor films to quinone derivatives, which underwent enolization to give fully conjugated hydroquinone polymers that displayed conductivities in the semiconductor regime.

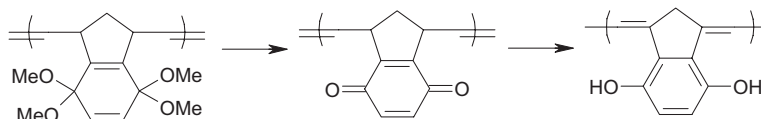


Fig. 3.4-22. Generation of a conjugated polymer from a *para*-quinone-derivatized precursor polymer.

Quinone/hydroquinone systems have a fairly complex redox chemistry, and, as expected, such systems have a complicated redox chemistry and electrochemistry.

3.4.6

Conclusions

In the synthesis of conjugated polymers, ROMP methodologies have a good track record of success in both direct and precursor routes. The features that make conjugated polymers fascinating technologically, conjugation and planarity, also often make them atmospherically sensitive, insoluble, infusible, and generally unattractive from a processing point of view. These factors have to be recognized in designing syntheses, and several very successful processes leading to the clean, well-defined materials required to advance this area of science and potential technology have been established. Progress requires open interdisciplinary interactions, and there can be little doubt that the continuous improvement of catalyst tolerance and reactivity will lead to further advances in this and other areas of polymer science.

References

- 1 D. CLOUTH, *Joseph Swan*, Gateshead Metropolitan Borough Council, Department of Education, 1979, ISBN 0 905977 07 6.
- 2 E. HUCKLE, *Z. für Phys.*, **1931**, 70, 204.
- 3 J. F. LENNARD-JONES, *Proc. Roy. Soc.*, **1937**, A158, 280.
- 4 H. C. LONGUET-HIGGINS AND L. SALEM, *Proc. Roy. Soc.*, **1959**, A251, 172.
- 5 G. NATTA, G. MAZZANTI AND P. CORRADINI, *Rend. Accad. Naz. Lincei CI Sc. Fis. Mat. E nat.*, **1958**, 25, 3.
- 6 D. J. BERETS AND D. S. SMITH, *Trans. Farad. Soc.*, **1968**, 823.
- 7 H. SHIRAKAWA AND S. IKEDA, *Polym. J.*, **1971**, 2, 231.
- 8 H. SHIRAKAWA, E. J. LEWIS, A. G. MACDIARMID, C. K. CHIANG AND A. J. HEEGER, *Chem. Commun.*, **1977**, 578; and C. K. CHIANG, C. R. FINCHER, Y. W. PARK, A. J. HEEGER, H. SHIRAKAWA, E. J. LEWIS, S. C. GAU AND A. G. MACDIARMID, *Phys. Rev. Lett.*, **1977**, 39, 1098.
- 9 H. NAARMANN AND N. THEOPHILOU, *Synth. Met*, **1987**, 22, 1; and J. TSUKAMOTO, A. TAKAHASHI AND K. KAWASAKI, *Japanese J. Appl. Phys*, **1990**, 29, 125.
- 10 Some of the earlier reviews and compilations are given here as possible useful starting points on the massive literature of the topic. *Electronic Properties of polymers and related compounds*, Eds H. KUZMANY, M. MEHRING AND S. ROTH, Springer Series in Solid-State Sciences 63, Springer-Verlag, **1985** and continuations in this series; *Handbook of Conducting Polymers*,

- 2 Volumes. Ed. T. A. SKOTHEIM, MARCEL DEKKER, Inc, New York, **1986** and supplements; N. C. BILLINGHAM AND P. D. CALVERT, *Electrically Conducting Polymers – A Polymer Science Viewpoint*, in *Advances in Polymer Science*, Springer-Verlag, **1989**, 90, 1–104; M. ALDISSI, *Inherently Conducting Polymers. Processing, Fabrication, Applications, Limitations*, Noyes Data Corporation, **1989**, 1–96; W. J. FEAST AND R. H. FRIEND, *Synthesis and material and electronic properties of conjugated polymers*, in *J. Mat Sci.*, **1990**, 25, 3796–3805; *Polyconjugated Materials*, Ed. G. ZERBI, North-Holland Press, **1992**; *Conjugated Polymers*, Eds. J. L. BREDAS AND R. SILBEY, Kluwer Academic Publishers, **1991**; *Conjugated Polymers and Related Materials. The Interconnection of Chemical and Electronic Structure*, Eds. W. R. SALANECK, I. LINDSTRÖM, B. RÅNBY, Oxford University Press, **1993**. W. J. FEAST, J. TSIBOUKLIS, K. L. POWWER, L. GROENENDAAL AND E. W. MEIJER, *Synthesis, processing and material properties of conjugated polymers, a Review*, *Polymer*, **1996**, 37, 5017–5047.
- 11 Y. V. KORSHAK, V. V. KORSHAK, G. KANISCHKA AND H. HÖCKER, *Macromol. Chem., Rapid Commun.*, **1985**, 6, 685.
 - 12 M. A. TLENKOPACHEV, Y. V. KORSHAK, A. V. ORLOV AND V. V. KORSHAK, *Dokl. Akad. Nauk SSSR*, **1986**, 291, 409.
 - 13 C. SCHAEVERIEN, J. DEWAN AND R. R. SCHROCK, *J. Am. Chem. Soc.*, **1986**, 108, 2771.
 - 14 J. KRESS, M. WESOLAK AND J. A. OSBORN, *Chem. Commun.*, **1982**, 514.
 - 15 F. L. KLAVETTER AND R. H. GRUBBS, *J. Am. Chem. Soc.*, **1988**, 110, 7807; idem, *Synthetic Metals*, **1989**, 28, D99–D104 and D105–D108; *Polym. Mater. Sci. Eng.*, **1988**, 58, 855.
 - 16 E. J. GINSBURG, C. R. GORMAN, R. H. GRUBBS, F. L. KLAVETTER, N. S. LEWIS, S. R. MARDER, J. W. PERRY AND M. J. SAILOR, in *Conjugated Polymeric Materials: Opportunities in Electronics, Optoelectronics and Molecular Electronics*, Eds J. L. BRÉDAS AND R. R. CHANCE, Kluwer Academic Publishers, **1990**, 65–81.
 - 17 E. J. GINSBURG, C. R. GORMAN, S. R. MARDER AND R. H. GRUBBS, *J. Am. Chem. Soc.*, **1989**, 111, 7621; *Angew. Chem. Adv. Mater.*, **1989**, 101, 1604.
 - 18 M. J. SAILOR, E. J. GINSBURG, C. R. GORMAN, R. H. GRUBBS, A. KUMAR, AND N. S. LEWIS, *Science*, **1990**, 249, 1146.
 - 19 M. J. SAILOR, F. L. KLAVETTER, R. H. GRUBBS AND N. S. LEWIS, *Nature*, **1990**, 155.
 - 20 T. H. JOZEFIAK, E. J. GINSBURG, C. R. GORMAN, M. J. SAILOR, R. H. GRUBBS AND N. S. LEWIS, *Proc. Soc. Plastics Engineers*, 1991.
 - 21 J. S. MOORE, C. R. GORMAN AND R. H. GRUBBS, *J. Am. Chem. Soc.*, **1991**, 113, 1704.
 - 22 C. R. GORMAN, E. J. GINSBURG, M. J. SAILOR, J. S. MOORE, T. H. JOZEFIAK, N. S. LEWIS AND R. H. GRUBBS, *Synthetic Metals*, **1991**, 41–43, 1033.
 - 23 T. H. JOZEFIAK, M. J. SAILOR, E. J. GINSBURG, C. R. GORMAN, N. S. LEWIS AND R. H. GRUBBS, *Proc. SPIE*, **1991**, 1463, 8.
 - 24 C. R. GORMAN, E. J. GINSBURG AND R. H. GRUBBS, *J. Am. Chem. Soc.*, **1993**, 115, 1397.
 - 25 T. H. JOZEFIAK, E. J. GINSBURG, C. R. GORMAN, R. H. GRUBBS AND N. S. LEWIS, *J. Am. Chem. Soc.*, **1993**, 115, 4705.
 - 26 O. A. SCHERMAN AND R. H. GRUBBS, *Synthetic Metals*, **2001**, 124, 431.
 - 27 T. M. SWAGER AND R. H. GRUBBS, *J. Am. Chem. Soc.*, **1987**, 109, 894.
 - 28 J. H. BURROUGHS, D. D. C. BRADLEY, A. R. BROWN, N. R. MARKS, K. MACKAY, R. H. FRIEND, P. L. BURNS AND A. B. HOLMES, *Nature*, **1990**, 347, 539.
 - 29 E. THORN-CSÁNYI AND H.-D. HÖHNK, *J. Mol. Cat.*, **1992**, 76, 101.
 - 30 E. THORN-CSÁNYI AND K. P. PFLUG, *Macromol. Chem.*, **1993**, 194, 2287.
 - 31 E. THORN-CSÁNYI, P. KRAXNER AND J. HAMMER, *J. Mol. Cat.*, **1994**, 90, 15.
 - 32 Y.-J. MIAO AND G. C. BAZAN, *Macromolecules*, **1994**, 27, 1063.
 - 33 Y.-J. MIAO AND G. C. BAZAN, *J. Am. Chem. Soc.*, **1994**, 116, 9379 and Y.-J.

- MIAO, B. J. SUN AND G. C. BAZAN, *Macromol. Symp.*, **1995**, 95, 185.
- 34 C. E. STANTON, T. R. LEE, R. H. GRUBBS, N. S. LEWIS, J. K. PUDELSKI, M. R. CALLSTROM, M. S. ERICKSON AND M. L. McLAUGHLIN, *Macromolecules*, **1995**, 28, 8713.
 - 35 F. STELZER, R. MUELNER, H. SCHLICK AND G. LEISING, in *Ring opening metathesis polymerization and related chemistry*, Eds E. KHOSRAVI AND T. SZYMANSKA-BUZAR, Kluwer Academic Publishers, **2002**, 185.
 - 36 E. THORN-CSÁNYI, in *Ring opening metathesis polymerization and related chemistry*, Eds E. KHOSRAVI AND T. SZYMANSKA-BUZAR, Kluwer Academic Publishers, **2002**, 295.
 - 37 K. WEISS AND C. WIRTH, in *Ring opening metathesis polymerization and related chemistry*, Eds E. KHOSRAVI AND T. SZYMANSKA-BUZAR, Kluwer Academic Publishers, **2002**, 341.
 - 38 J. H. EDWARDS AND W. J. FEAST, *Polymer*, **1980**, 595.
 - 39 J. H. EDWARDS, W. J. FEAST AND D. C. BOTT, *Polymer*, **1984**, 25, 395.
 - 40 D. C. BOTT, C. K. CHAI, J. H. EDWARDS, W. J. FEAST, R. H. FRIEND AND M. E. HORTON, *J. de Physique*, **1983**, 44, C3–143.
 - 41 W. J. FEAST AND J. N. WINTER, *Chem. Commun.*, **1985**, 202.
 - 42 D. C. BOTT, C. S. BROWN, J. H. EDWARDS, W. J. FEAST, D. PARKER AND J. N. WINTER, *Mol. Cryst. Liq. Cryst.*, **1985**, 117, 9.
 - 43 R. H. FRIEND, D. C. BOTT, D. D. C. BRADLEY, C. K. CHAI, W. J. FEAST, P. J. S. FOOT, J. R. M. GILLES, M. E. HORTON AND P. D. TOWNSEND, *Phil. Trans. R. Soc. London*, **1985**, A313, 37.
 - 44 W. J. FEAST, D. PARKER, J. N. WINTER, D. C. BOTT AND N. S. WALKER, *Springer Series in Solid State Science*, Eds H. KUSMANY, M. MEHRING, S. ROTH, Springer-Verlag, **1985**, 63, 45.
 - 45 D. C. BOTT, C. S. BROWN, C. K. CHAI, N. S. WALKER, W. J. FEAST, P. J. S. FOOT, P. D. CALVERT, N. C. BILLINGHAM AND R. H. FRIEND, *Synthetic Metals*, **1986**, 14, 245.
 - 46 W. J. FEAST, M. J. TAYLOR AND J. N. WINTER, *Polymer*, **1987**, 28, 593.
 - 47 P. C. ALLEN, D. C. BOTT, C. S. BROWN, L. M. CONNORS, S. GRAY, N. S. WALKER, P. I. CLEMENSON AND W. J. FEAST, *Springer Series in Solid State Science*, Eds H. KUSMANY, M. MEHRING, S. ROTH, Springer-Verlag, **1989**, 91, 456.
 - 48 C. A. JONES, R. A. LAURENCE, J. MARTENS, R. H. FRIEND, D. PARKER, W. J. FEAST, M. LÖGDIUND AND W. R. SALANECK, *Polymer*, **1991**, 32, 1200.
 - 49 W. J. FEAST, *Phil. Trans. R. Soc. London*, **1990**, A330, 117.
 - 50 P. I. CLEMENSON AND W. J. FEAST, M. M. AHMAD, P. C. ALLEN, D. C. BOTT, C. S. BROWN, L. M. CONNORS, N. S. WALKER AND J. N. WINTER, *Polymer*, **1992**, 33, 4711.
 - 51 J. H. F. MARTENS, K. PICHLER, E. A. MARSEGILIA, R. H. FRIEND, H. CRAMAIL AND W. J. FEAST, *Synthetic Metals*, **1993**, 55–57, 449.
 - 52 J. H. F. MARTENS, K. PICHLER, E. A. MARSEGILIA, R. H. FRIEND, H. CRAMAIL, E. KHOSRAVI, D. PARKER AND W. J. FEAST, *Polymer*, **1994**, 35, 403.
 - 53 G. WIDAWSKI, W. J. FEAST AND P. DOUNIS, *J. Mater. Chem.*, **1995**, 5, 1847.
 - 54 P. DOUNIS, W. J. FEAST AND G. WIDAWSKI, *J. Mol. Cat. A.*, **1997**, 115, 51.
 - 55 F. L. KLAFFETTER AND R. H. GRUBBS, *Synthetic Metals*, **1988**, 26, 311.
 - 56 F. STELZER, O. LEITNER, K. PRESSL, G. LEISING AND R. H. GRUBBS, *Synthetic Metals*, **1991**, 41–43, 991.
 - 57 F. STELZER, R. H. GRUBBS AND G. LEISING, *Polymer*, **1991**, 32, 1851.
 - 58 R. R. SCHROCK, *Acc. Chem. Res.*, **1990**, 23, 158.
 - 59 J. H. BURROUGHS, C. A. JONES AND R. H. FRIEND, *Nature*, **1988**, 335, 137.
 - 60 J. H. BURROUGHS AND R. H. FRIEND, in *Conjugated Polymers*, Eds J. L. BREDAS AND R. SILBEY, Kluwer Academic Publishers, **1991**, 555.
 - 61 T. M. SWAGER, D. A. DOUGHERTY AND R. H. GRUBBS, *J. Am. Chem. Soc.*, **1988**, 110, 2973.
 - 62 T. M. SWAGER AND R. H. GRUBBS, *J. Am. Chem. Soc.*, **1989**, 111, 4413.
 - 63 W. J. FEAST, in *Ring opening metathesis polymerization and related chemistry*, Eds E. KHOSRAVI AND T. SZYMANSKA-

- BUZAR, Kluwer Academic Publishers, **2002**, 177.
- 64** S. TASCH, W. GRAUPNER, G. LEISING, LIN PU, M. W. WAGNER AND R. H. GRUBBS, *Adv. Mater.* **1995**, 7, 903.
- 65** LIN PU, M. W. WAGAMAN, R. H. GRUBBS, *Macromolecules*, **1996**, 29, 1138.
- 66** M. W. WAGAMAN, R. H. GRUBBS, *Macromolecules*, **1997**, 30, 3978.
- 67** W. J. FEAST AND K. HARPER, *Brit. Polymer J.*, **1986**, 18, 161.
- 68** T. M. SWAGER, M. M. ROCK AND R. H. GRUBBS, *New Polymeric Materials*, **1990**, 2, 1.

3.5

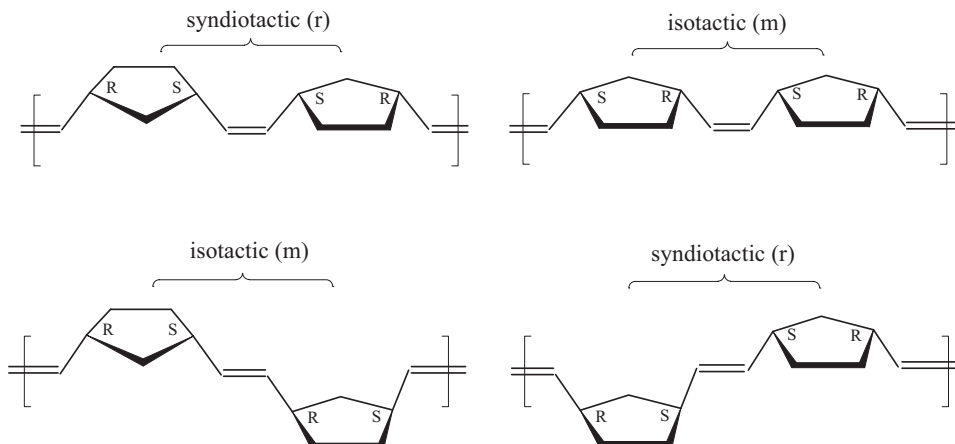
Stereochemistry of Ring-Opening Metathesis Polymerization

James G. Hamilton

3.5.1

Introduction

Polymers formed in ring-opening metathesis polymerization (ROMP) reactions differ from the products of all other olefinic polymerizations in that the double bonds that mediate the polymerization reappear in the polymeric product, the newly formed double bonds may be *cis* (c) or *trans* (t), and the c/t ratio is often seen as the primary microstructural variant. In addition, whenever chiral or prochiral monomers are polymerized, the tacticity of the polymer, arising from the sequence of chiral atoms along the polymer chain, must also be taken into account. The four stereochemical variations that are possible for monomer dyad units in the archetypal polymers formed from bicyclo[2.2.1]hept-2-ene (norbornene) are depicted in Scheme 3.5-1. ROMP polymer microstructure is therefore more complex than that found with polymers formed via free-radical, ionic, or other coordination polymerizations of cyclic olefins.



Scheme 3.5-1. Different possible combinations of dyad tacticity and double-bond stereochemistry in poly(norbornene).

It is often difficult to delineate the effects that derive from different combinations of these two stereochemical features, yet both are important because they combine to control the conformation of the polymer chain and hence determine many of the properties of the materials in the solid state and in solution. Therefore, the ability to obtain a precise analysis of the polymers is paramount because it leads ultimately to an understanding of the factors that control polymer stereochemistry. To this end, extensive use has been made of ^{13}C NMR and to a lesser extent ^1H NMR spectroscopy, which has permitted an assessment of the polymers' c/t ratio and, in a number of cases, the proportions of syndiotactic (r) and isotactic (m) dyads, as well as the distribution of these features.

A good degree of control over microstructure has been achieved with the classical, or metal salt-type, catalyst systems, but the fact that one can vary the steric and electronic properties of the site in such a controlled and systematic way with the new-generation metallocarbenes, coupled with their current availability, means that extensive use is now made of these systems. Consequently, it is here that the emphasis is placed in the following overview. A strong emphasis is also placed on polymers formed from norbornene and its derivatives, which provide many useful substrates for ROMP reactions due to their accessibility and also to the special reactivity of the norbornene ring system. One can now form polymers with practically any functionality appended to the main chain so long as it can be attached to the norbornene skeleton. The high reactivity also means that one can study polymer formation using even quite unreactive, but often interesting, catalyst systems [1]. There is, however, no stereochemical panacea, and this will be clear from what follows. Although some generalizations can be made, the stereoselectivity with a given catalyst is often monomer dependent and it is therefore prudent to consider each catalyst/monomer combination separately.

The review covers a period from the mid-1970s, when the first NMR spectra of ROMP polymers were examined, to the present and traces the advances in both the stereoselectivity of the catalysts and the spectroscopic analysis of the polymers, which has led not only to a detailed knowledge of polymer microstructure but also to an in-depth understanding of many aspects of the reaction mechanism. A brief summary of the consequences of stereoisomerization in ROMP is followed by a review of the methods used for the analysis of the polymers, and the chapter concludes with an overview of mechanistic aspects of stereoselectivity in ROMP.

3.5.2

Consequences of *cis/trans* Isomerism and Tacticity in ROMP Polymers

The relationship between the c/t ratio and the solid-state and solution properties of ROMP polymers is well established and is perhaps best demonstrated with linear polyalkenamers, where tacticity is not an issue and where we are looking simply at the effects of c/t ratio. Some general trends are noted. The melting point of polyalkenamers is dependent not only on the double-bond density, which derives from the ring size of the starting monomer, but also on the c/t ratio, as is shown for a

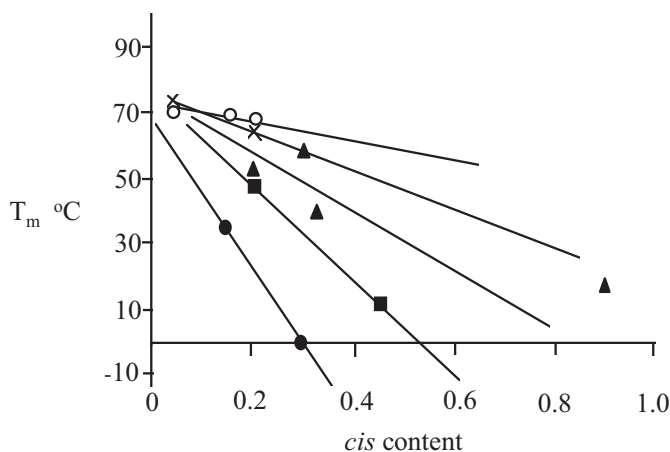


Fig. 3.5-1. Melting temperatures, T_m , of polyalkenamers versus *cis* double-bond content for a series of polyalkenamers formed from ○, cyclododecene; ×, cyclodecene; ▲, cyclooctene; ■, cycloheptene; ●, cyclooctadiene. (Reprinted from *Polymer*, Vol. 36, P. Dounis, W. J. Feast, A. M. Kenwright, "Ring-Opening

Metathesis Polymerization of Monocyclic Alkenes using Molybdenum and Tungsten Alkylidene (Schrock-type) Initiators and ^{13}C Nuclear Magnetic resonance Studies of the Resulting Polyalkenamers" 2787–2796, Copyright 1995, with permission from Elsevier Science.)

series of polyalkenamers formed using well-defined molybdenum and tungsten initiators (Figure 3.5-1) [2]. This trend is also followed by glass transition temperatures, T_g , with high *cis* poly(pentenamer) (poly(cyclopentene)) having the lowest T_g of all polymers in the hydrocarbon series [3]. The rate of polymer crystallization slows dramatically with even very small increases in the *cis* content, as, for example, in the much studied *trans* poly(cyclopentene) [4], where increasing the *cis* content by only 4% produces an almost sixfold increase in the $t_{1/2}$ of crystallization. For the same type of polymer in solution, higher $[\eta]/M$ values were found for the linear, less flexible *trans* polymer than for the more coiled *cis* polymer [5]. In this context, and important from the point of view of widely used size-exclusion chromatography methods of MW determination, is the fact that retention times may be different for polymers of the same MW but with different *c/t* ratios [6].

C/t ratios are also important in determining the properties of polymers with conjugated double bonds, notably the polyacetylene series. Frequently, the examples that have been prepared using ROMP are of high or medium *cis* content, but these then undergo *c/t* isomerism. The Durham route to polyacetylene involves the thermal elimination of a benzene derivative from a soluble high-*cis* precursor polymer with subsequent or simultaneous *c-to-t* isomerization (depending on the chemical structure of the precursor) to form *trans* polyacetylene films [7]. Polyacetylene may also be formed directly by the ROMP of cyclooctatetraene using both classical [8] and well-defined tungsten catalysts [9]. Again, the initial product of these reactions is predominantly the *cis* isomer, but facile isomerism to the more planar *trans* isomer yields materials that, after doping, are electrically conductive.

Alkyl-substituted *cis* poly(cyclooctatetraenes) are soluble in a number of common solvents, and those bearing the more bulky substituents remain soluble even after isomerism to the *trans* form, which greatly facilitates the study of these materials [10].

Water-soluble forms of these materials may be synthesized by dehydrogenation of ROMP polymers prepared from either 7-oxanorbornadiene [11] or barrelene [12] derivatives that bear polar functional groups. Although polymers formed from the latter monomer apparently undergo *cis*-to-*trans* isomerization during dehydrogenation, the former can retain a high *cis* content, which is reflected in the λ_{max} of their dilute solutions. Thus, solutions of ~50% *cis* polymers are red but quickly become deep purple on exposure to sunlight, the red shift being the result of facile isomerization to the more planar all-*trans* form, which accommodates an increased conjugation length. The nature of the color changes observed as the pH of their solutions is varied is also dependent on the c/t ratio [11].

A number of reports have appeared in the literature in which various other properties have been related to the polymers' c/t ratio. These include gas transport [13], liquid crystalline behavior [14], the specific rotation of optically active polymers [15], and the dimensions of two-dimensional monolayers [16]. Generally, the different properties can be attributed to a condensed morphology for high *cis* content polymers compared to a more extended morphology of the high *trans* materials, but one should caution against attributing polymer properties solely to c/t effects whenever the complimentary tacticity parameter has not been determined. The importance of this is highlighted by recent theoretical studies in which different isomerically pure forms of some substituted poly(norbornene)s are modeled [17], and these studies show how the chain morphology can be affected both by c/t ratio and tacticity. Unfortunately, there is practically no information in the literature on how the macroscopic properties of the polymers depend on tacticity effects alone. This has been partly due to the difficulty in preparing samples with only one type of double bond that are sufficiently either syndiotactic or isotactic to allow comparisons to be made; one may expect the situation to be resolved as new catalysts are developed and such materials become available.

3.5.3

Determination of the Stereochemistry of ROMP Polymers

3.5.3.1

Cis/trans Double-Bond Ratio

When polymers are prepared from novel monomers or by using new catalyst systems, almost the first question that arises concerns the c/t ratio, as this has a bearing on both the properties of the polymer as a material and the stereoselectivity of the catalyst. In principle, both vibrational spectroscopy and NMR can be used, and although the latter has found by far the widest application, IR and Raman techniques are useful in that insoluble samples are amenable to analysis.

One can also get a rapid estimate of the overall stereochemistry using the =C–H out-of-plane deformation bands, although the *cis* ($\sim 720\text{ cm}^{-1}$) is relatively a somewhat weaker absorption than the *trans* ($\sim 965\text{ cm}^{-1}$) [18], and for quantitative work calibration is necessary [1d, 15a]. The technique is of less value when functional groups are present, as peaks from these often obscure the main *cis* and *trans* peaks. IR spectroscopy is also very valuable as an adjunct to NMR spectroscopy, as it allows one to be certain of the assignment of *cis* and *trans* resonances in new polymers. The complimentary technique of Raman spectroscopy lends itself to the examination of unconventional samples using fiber optic technology, and these advantages have been used recently both to monitor ROMP reactions [19] and to determine c/t ratios of thin films formed by vapor deposition ROMP [20].

Although other physical methods have been used in specific cases to determine polymer microstructure (*vide infra*), NMR spectroscopy of polymer solutions, especially ^{13}C NMR, is undoubtedly the most powerful method available for this analysis; solid-state NMR is rarely used. While ^1H NMR has the advantage of small sample requirement and the facility to collect enough data within a relatively short time to yield usable spectra, distinct *cis* and *trans* signals are not always resolved and the method tends to view the polymer as if the repeating units were isolated entities; therefore, little information is obtained concerning stereochemical sequences along the polymer chain. This is not the case with ^{13}C NMR spectroscopy, where chemical shifts are usually sensitive to quite remote structural variations and the peak intensities can be used directly to measure c/t ratio and tacticity, differences in the NoE effect for similar carbon atoms being minimal [21].

^{13}C NMR spectroscopy was first applied to metathesis polymers some years ago in a series of studies aimed at developing a mechanistic picture of the propagation reaction. Most of the original work was carried out with the archetypal poly(norbornene), and a spectrum of a fairly typical, medium *cis* content polymer is reproduced in Figure 3.5-2.

The first step in the analysis of such a spectrum is to locate the main *cis* and *trans* resonances, and it is thus highly desirable to have available high *cis* and high *trans* variants so that one can use the spectra of these to fix the position of the *cis* and *trans* lines. Stereospecific catalyst systems that can yield these polymers are described in Section 3.5.4, and IR spectroscopy can be used to confirm their stereochemistry. *Cis* and *trans* olefinic carbons are usually well separated, and the largest difference is found with the allylic carbon atoms, where the *trans* signal is invariably about 4 ppm downfield from the *cis*, a fact recognized with so many polymers that it is now used in routine assignment of stereochemistry. This does not apply to the line positions of other signals, but these too are determined by their proximity to *cis* and *trans* double bonds.

As is evident from inspection of the spectrum of poly(norbornene) (Figure 3.5-2), line positions are sensitive not only to the stereochemistry of the double bond of a particular repeating unit but also to the next nearest double bond along the chain. This gives rise to a set of four lines, cc, ct, tc, and tt, for each unsymmetrically placed carbon of the cyclopentyl ring. With the symmetrically placed C^7 , the ct and tc environments are identical and a triplet results.

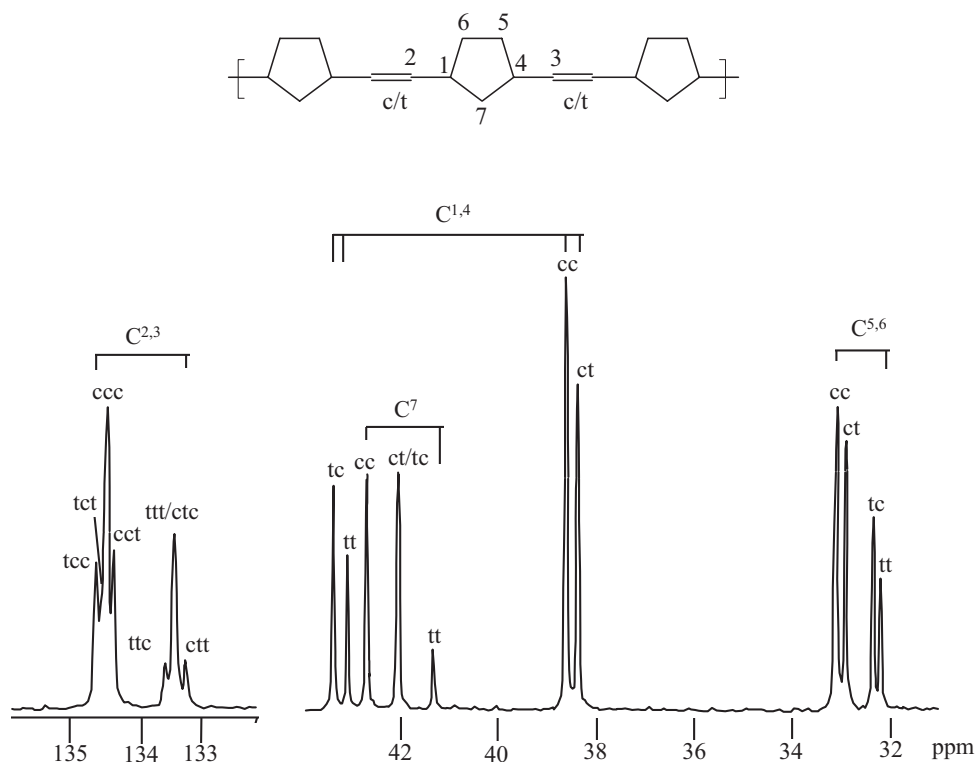


Fig. 3.5-2. ^{13}C NMR spectrum of a 60% *cis* sample of poly(norbornene) showing the sensitivity of line positions to double-bond stereochemistry (Reprinted from *Ring-Opening Metathesis Polymerization and Related Chemistry*; NATO Science series II: *Mathematics, Physics*

and Chemistry – Vol. 56, V. Emir-Ebrahimi, J. G. Hamilton, J. J. Rooney, *Blockiness and Tacticity in Metathesis Polymers*, Copyright 2002, with permission from Kluwer Academic Publishers, Amsterdam).

In many medium to high *cis* content polymers, the *cc* and *tt* signals for a given carbon are more intense than the *ct* component, that is, more than would be expected on the basis of a random distribution, which means that the different double bonds have a tendency to be distributed in blocks. The mechanistic implications of this are discussed in Section 3.5.4.1.

The best-quality ^{13}C NMR spectra of poly(norbornene) show that the olefinic carbons are sensitive to double-bond triad sequences, which is important because it allows one to study the frequency of the occurrence of different double-bond triads and gain further insight into the propagation mechanism; again, this is examined in more detail in Section 3.5.4.1. These latter features also appear in the spectra of polymers formed from monocyclic olefins, and double-bond triad structures are resolved in polymers up to poly(cyclooctene). Thereafter, the double bonds are too remote to produce an observable effect [2].

Although substituents will cause substantial differences in the appearance of

individual spectra, this scheme of analysis applies to all polymers with symmetrical repeat units. However, many polymers have unsymmetrical repeat units and substituents are usually orientated in a random manner along the chain, giving rise to head-to-head (HH), head-to-tail (HT), and tail-to-tail (TT) signals in their spectra, each of which may again be split into *cis* and *trans* components [22, 23].

It can be difficult to determine the c/t ratio and distribution in many other interesting polymers where these parameters may have a bearing on polymer properties; this is particularly the case with the numerous comb- or brush-type structures, where the main chain can become relatively immobile and, in some instances, almost NMR silent.

3.5.3.2

Tacticity

After fine structure from c/t (and HT, TT, and HH) effects has been taken into account, additional fine structure can arise only from tacticity. However, this does not imply a “fine structure hierarchy” in terms of the magnitude of the effects, and one must be alert to the fact that tacticity splittings are sometimes greater than those due to c/t effects and that this may vary even within the spectrum of one polymer. Although usable tacticity splittings are not seen in the spectra of poly(norbornene), which at best shows only broadening of certain *cis* lines [24], high *cis* poly(norbornadiene) (Figure 3.5-3) has a single olefinic line sufficiently split to be useful in tacticity determination [25]; the spectra of *trans* polymers do not show this effect, reflecting a greater conformational flexibility. The proximity of chiral centers is important, and while the spectrum of poly(4-methyl-cyclopentene) is unaffected by tacticity [26], that of poly(3-methylcyclobutene), where the chiral centers can be closer together (in HH and HT structures), apparently does show the effect [27].

Hydrogenation of ROMP polymers has proved to be a useful technique in tacticity determination because the saturated derivatives frequently exhibit tacticity fine structure when that of the unsaturated parent does not [28]. The relative configurations of the chiral carbon atoms along the chain, from which m and r structures derive, are fixed during the propagation reaction and are maintained on hydrogenation so that the tacticity of these derivatives is directly related to that of the unsaturated precursors. Another aspect of this procedure is that it can be useful in the analysis of complex spectra because one can access retrospectively whether some of the fine structure in the original polymer arises from tacticity effects. Although the method has found wide applicability, a limitation is that it is of less value as the c/t ratio approaches unity because the important relationship between tacticity and double-bond stereochemistry (Section 3.5.4.2) is lost on hydrogenation. One cannot distinguish, for example, between a 50% *cis* polymer in which the *cis* junctions are exclusively syndiotactic and *trans* exclusively isotactic, that is, an essentially tactic polymer, and a stereochemically random polymer; both would appear to be atactic on hydrogenation. In certain environments *cis* double bonds have proved difficult to hydrogenate. These include the head-

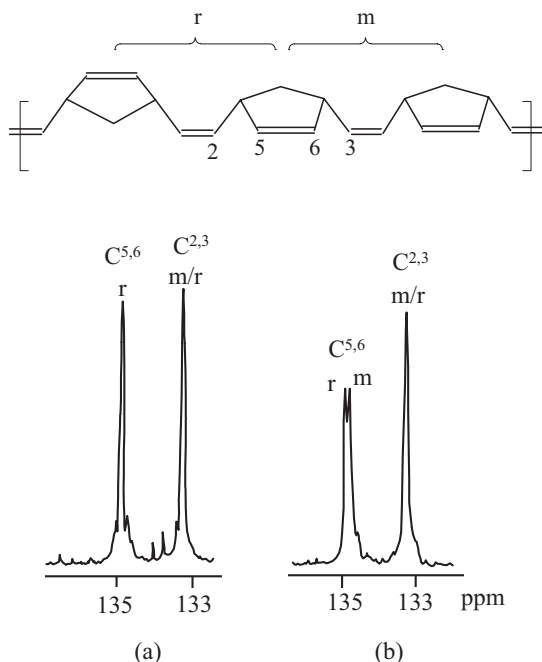


Fig. 3.5-3. The olefinic region of the ^{13}C NMR spectra of two samples of all-*cis* poly(norbornadiene), (a) syndiotactic polymer made using OsCl_3 /phenylacetylene, (b) atactic polymer made using $\text{WCl}_6/\text{Me}_4\text{Sn}$ /dioxan (Reprinted from *Ring-Opening Metathesis Polymerization and Related Chemistry*; NATO

Science series II: *Mathematics, Physics and Chemistry* – Vol. 56, V. Emir-Ebrahimi, J. G. Hamilton, J. J. Rooney, *Blockiness and Tacticity in Metathesis Polymers*, Copyright 2002, with permission from Kluwer Academic Publishers, Amsterdam).

to-head units in poly(5,5-dimethylnorbornene) [29] and in highly tactic poly(7-methylnorbornene) [30]; the *trans* double bonds in these polymers hydrogenate normally.

Symmetrical placement of alkyl substituents in norbornene [22, 31, 32] and norbornadiene [33] produces a remarkable effect in the ^{13}C NMR spectra of their polymers. Fine structure now appears on many of the *cis* and *trans* lines, which is due to tacticity effects, commonly at the monomer triad level. The C^7 resonance (Figure 3.5-4) in the spectra of some of these polymers is a good illustration of this and also of how the precise nature of the line splitting can be affected by small changes in chemical structure of the repeating unit. In each polymer C^7 is primarily a triplet due to c/t effects, but it will be noted that while in polymers formed from the diene the tt line is resolved into a triplet ($t_r t_r$, $t_r t_m$, $t_m t_m$) and the *cis* line is unaffected (Figure 3.5-4c), the monoene polymer, (Figure 3.5-4b) has the splitting pattern reversed. This is a fairly common phenomenon and highlights a general problem of line assignment, i.e., that each polymer needs to be considered as a separate case.

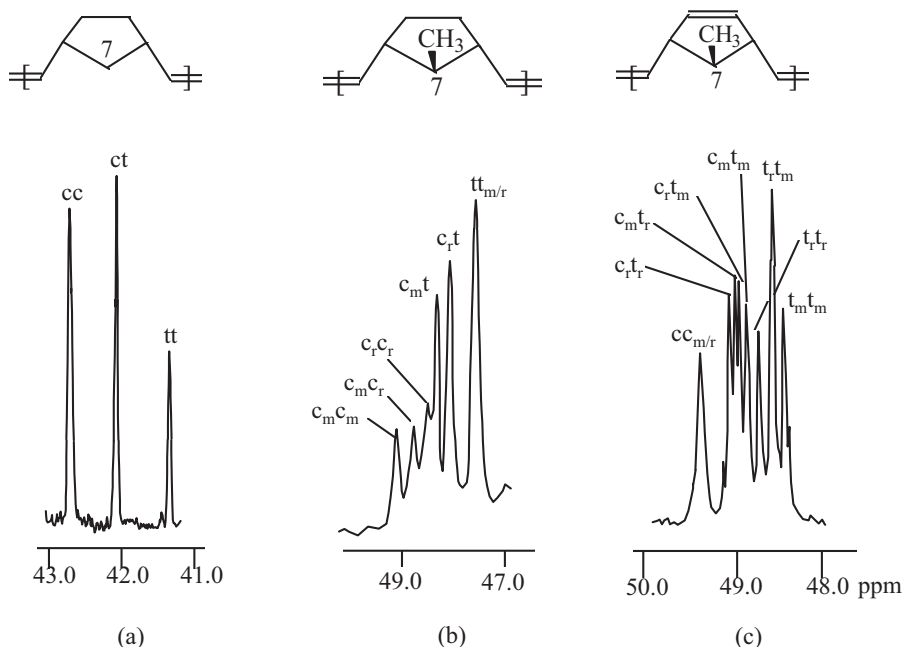
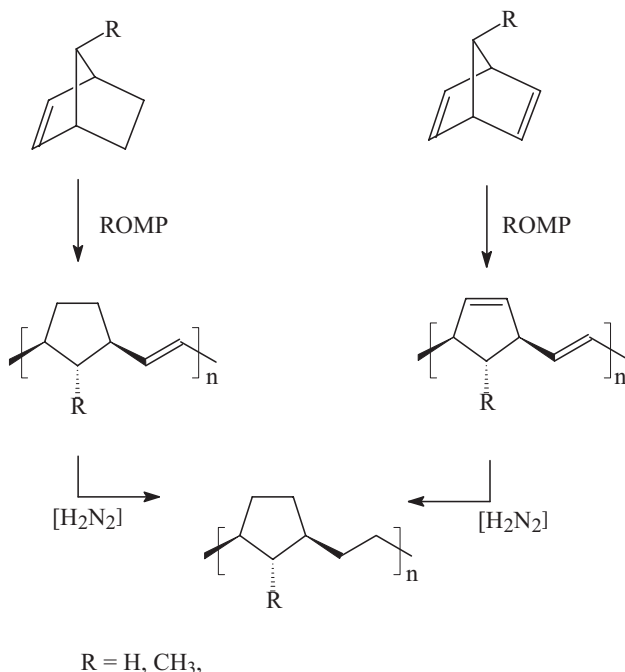


Fig. 3.5-4. The C^7 carbon signal in the ^{13}C NMR spectra of (a) poly(norbornene), (b) poly(7-methylnorbornene), and (c) poly(7-methylnorbornadiene) showing the effects of methyl substitution on tacticity fine structure. (c Reprinted from *J. Organomet.*

Chem., Vol. 606, J. G. Hamilton, U. Frenzel, F. J. Kohl, T. Weskamp, J. J. Rooney, W. A. Herrmann, O. Nuyken, "N-Heterocyclic Carbenes (NHC) in Olefin Metathesis: Influence of the NHC-Ligands on Polymer Tacticity", 8–12, Copyright 2000, with permission from Elsevier Science.)

As with poly(norbornene) and poly(norbornadiene), hydrogenation of these methyl-substituted derivatives yields the same repeating unit (Scheme 3.5-2), and this allows one to compare the tacticity of polymers formed from the two monomer types [33]. The correlation is also possible with polymers formed from *exo*, *exo*-5,6-diester derivatives of norbornene and the analogous norbornadiene derivative, where hydrogenation of the latter occurs regiospecifically so that both polymers yield the same saturated repeating unit upon hydrogenation [34]. Although initially developed using first-generation catalysts, the use of these methyl derivatives has now been applied to polymers formed with a number of well-defined catalyst systems [30, 35].

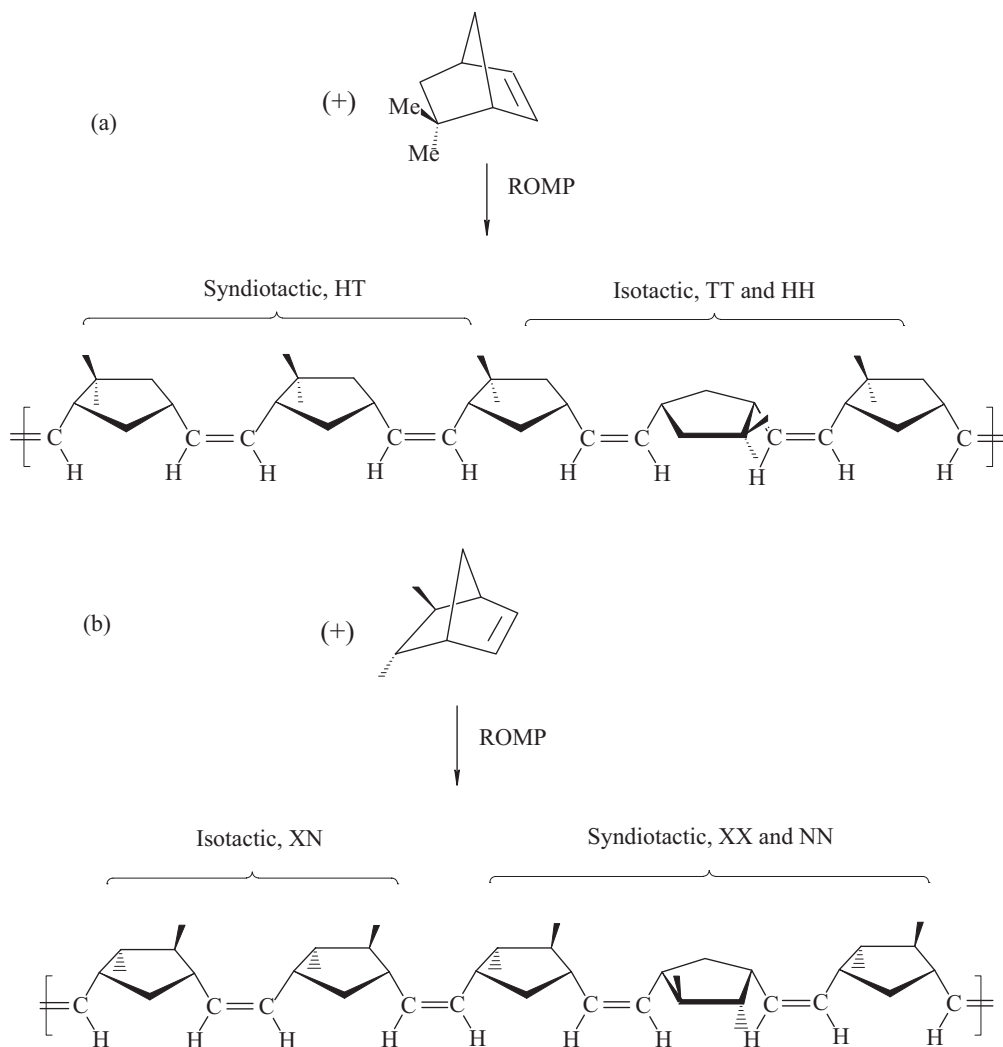
The assignment of *m* or *r* stereochemistry to the individual lines in the spectra of polymers formed from symmetrical monomers such as those above cannot be made directly because there is no absolute method, apart, potentially, from correlations with X-ray structures of appropriate polymers, for making such assignments. Assignments must therefore be made indirectly based on the assumption that certain "cornerstone" catalyst systems will consistently yield polymers of a specific tacticity, the behavior of these catalysts being extrapolated from cases



Scheme 3.5-2. Use of hydrogenation in the correlation of tacticity of ROMP polymers of norbornene, norbornadiene, and their 7-substituted derivatives.

where m and r tacticity can be determined with certainty, that is, by the use of resolved chiral monomers.

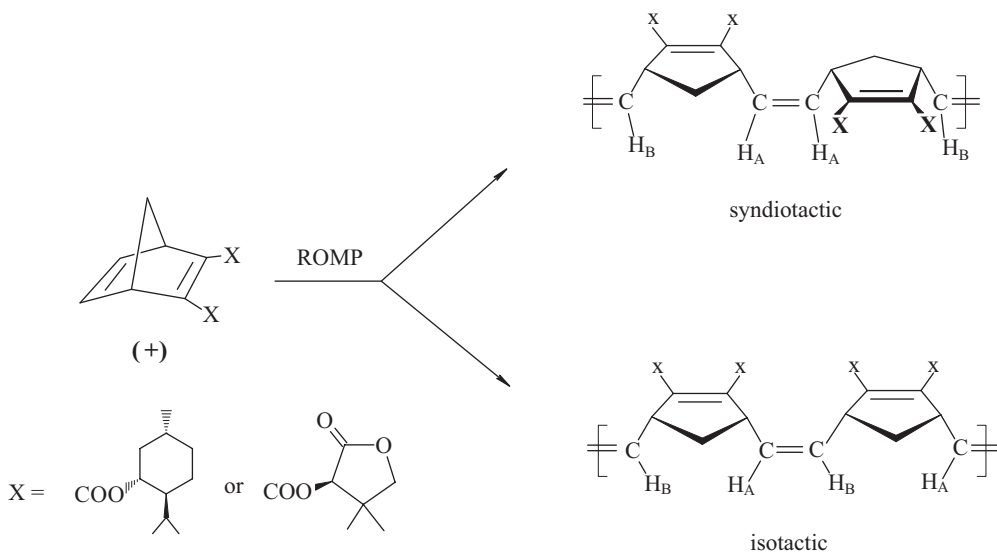
The use of such monomers (unsymmetrically substituted norbornenes) was pioneered in the seminal studies of Ivin and Rooney, who recognized that the tacticity of polymers formed from single enantiomers of the monomer would be translated into an orientational bias (HT or HH, TT) of the substituents along the polymer chain. The method relies on there being little or no bias present in polymers formed from the racemic monomer and is applicable to polymers formed from all unsymmetrically 5 or 6-substituted norbornene derivatives, as long as the relevant lines are resolved in the spectra. The method was applied to polymers formed from (+)-exo-5-methyl [36] and (+)- or (−)-5,5-dimethylnorbornene [37] (Scheme 3.5-3a); isotactic polymers are necessarily HT biased and syndiotactic polymers are HH (TT) biased, independent of the double-bond stereochemistry. Although both monomers were used, the resolution of signals from HH, HT, and TT units, for both *cis* and *trans* double bonds, was superior with the dimethyl derivative; the important consequence of this was that tacticity could be determined for every stereochemical permutation. Polymers formed from optically active endo-exo-5,6-dimethylnorbornene have also been utilized in this way [38], and the bias is now seen as the relative configuration of the methyl substituents across the double



Scheme 3.5-3. Use of single enantiomers of (a) 5,5-dimethylnorbornene and (b) *exo,endo*-5,6-dimethylnorbornene in the determination of the tacticity of their polymers

bonds leading to an *exo-exo* (XX) and an *exo-endo* (XN) bias as shown in Scheme 3.5-3b. ^{13}C NMR spectroscopy of the polymers formed from either the (+) or (−) enantiomer of these monomers showed a wide variation in the overall orientational bias, and hence the tacticity, of polymers formed using a wide range of first-generation catalysts [37], as well as some well-defined molybdenum catalysts [38].

The method may be used whenever optically active forms of a monomer are available. For example, optically active 7-oxanorbornene derivatives, available

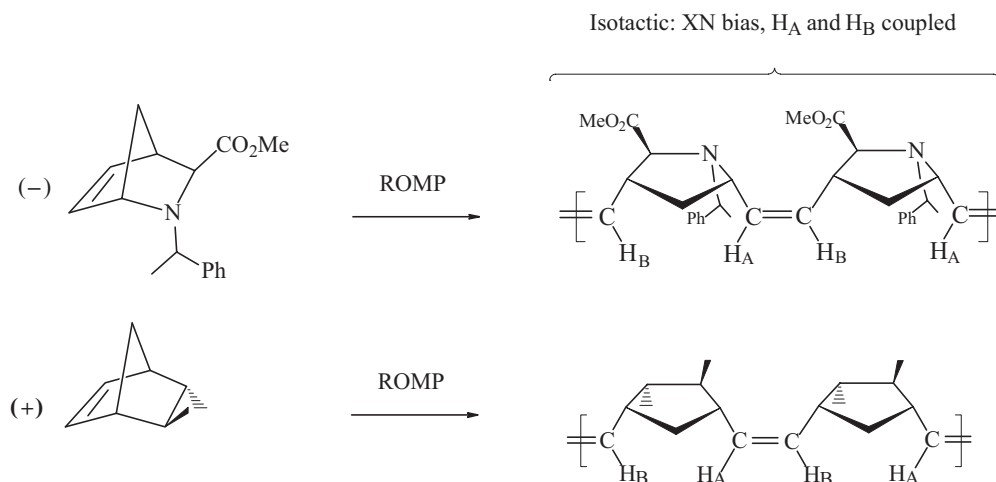


Scheme 3.5-4. Detection of syndiotactic (H_A and H_B not coupled) and isotactic (H_A and H_B coupled) dyads in polymers formed from optically active norbornadiene derivatives.

through enzymatic resolution [39], could be used to determine the tacticity of biologically active neoglycopolymers [40], where knowledge of tacticity, and double-bond stereochemistry, would be important in studying the interactions of these polymers with cellular substrates.

A related method of tacticity determination uses two-dimensional ^1H NMR techniques and has been demonstrated with polymers formed from norbornadiene derivatives that were symmetrically substituted with optically active ester groups, the chiral alcohol moiety of which is readily available in optically pure form, thereby avoiding a tedious resolution of enantiomers (Scheme 3.5-4) [17a]. The ^1H NMR spectra of these polymers show two resolved signals for the olefinic protons, H_A and H_B . The symmetry of the different dyad units dictates that in syndiotactic dyads, these protons reside on different double bonds and are therefore not coupled, but they are coupled in isotactic dyads, where they are on the same double bond. The coupling can be detected by using a COSY experiment, but the method may be applicable only to fairly stereochemically pure forms of appropriate polymers because potential overlap of lines would make coupling difficult to detect. This method has also been applied to optically active 5,6-disubstituted norbornenes [17a] and to an analogous azanorbornene derivative [41], where the tacticities that were thus determined check out against those obtained by using the XN or XX, NN bias observed in the ^{13}C NMR spectra of polymers formed from the resolved monomers (Scheme 3.5-5).

Perhaps less generally applicable to tacticity determination are certain physical



Scheme 3.5-5. Combination of ¹³C and ¹H NMR techniques provides a crosscheck in the determination of tacticity.

methods that depend on the morphology that high *cis* or *trans* polymers adopt depending on their tacticity. For example, properties that rely on the correct alignment of substituents appended to a poly(norbornene) backbone with appropriate stereochemistry have been used to determine tacticity when the NMR methods described above are not applicable. These include enhanced hyperpolarizability and relaxed dielectric constant measurements. In the former case, enhanced hyperpolarizability was noted for the high *trans* polymers formed from a series of monomers bearing conjugated dipolar substituents. The enhancement was believed to result from the alignment of the chromophores, which is possible with a syndiotactic but not an isotactic stereochemistry [17c]. Although not primarily intended as method of determining tacticity, the photochemical behavior of certain norbornyl ketals was explained similarly [17d].

The sense in which dipolar moieties can align at temperatures above *T_g* has been related to the tacticity of the backbone and is reflected in the magnitude of relaxed permittivities and dipole moments of the particular material. High *trans* polymers prepared from 2,3-bis(trifluoromethyl)norbornadiene show much higher values than the high *cis* forms. Both polymers are thought to be highly tactic from their ¹³C NMR spectra, but the specific type of tacticity cannot be determined by the NMR method. Consideration of models that represent the different specific stereochemistries reveals that dipoles associated with successive repeating units in *trans* polymers are all aligned in the same direction, but only when the polymer is syndiotactic, leading to large dipole moments. The dipoles in successive repeating units of *cis* polymers are opposed and would give low dipole moments only when the polymer is syndiotactic. The dielectric properties of the two polymers were thus rationalized on the basis of their syndiotacticity [42].

3.5.4

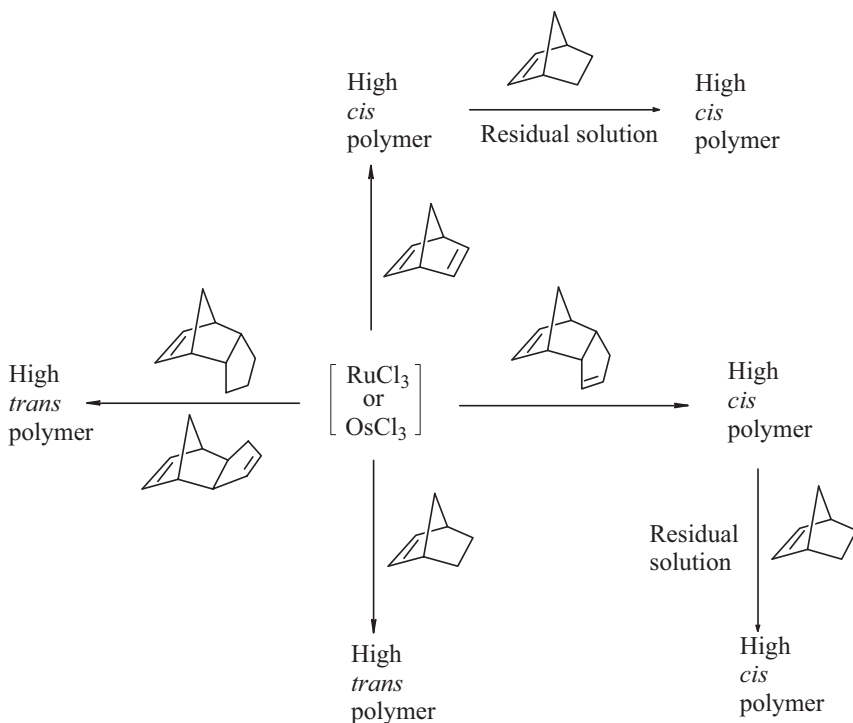
Control and Interpretation of Stereochemistry

3.5.4.1

Ratio and Distribution of *cis* and *trans* Double Bonds

A substantial degree of stereochemical control is possible when using the first-generation ROMP catalysts [1b]. For example, OsCl_3 and especially RuCl_3 have traditionally been used to prepare high *trans* polymers, and ReCl_5 yields high *cis* polymers that are often highly syndiotactic, although the activity of different samples can be highly variable; recently, the more reliable and robust OsCl_3 /phenylacetylene system [28] has been used instead of ReCl_5 .

It will become apparent, as the behavior of all the catalyst types is examined, that the monomer can strongly influence c/t ratios. An excellent example of this is seen with the classical RuCl_3 and OsCl_3 catalysts, which atypically yield high *cis* polymers with chelating monomers such as endo-dicyclopentadiene and norbornadiene (Scheme 3.5-6); norbornene and the exo isomer of dicyclopentadiene, as well as numerous other monomer types, give high *trans* materials. Chelation of the diene, which is believed to be responsible for the effect by providing steric con-



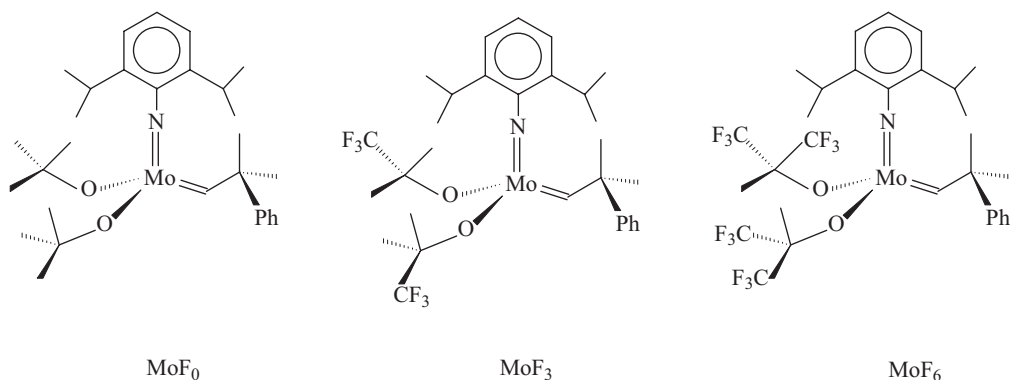
Scheme 3.5-6. Effect of double-bond chelation at catalyst sites derived from classical noble metal catalysts.

straints at the site, is demonstrated by the fact that poly(norbornene) prepared in the presence of endo-dicyclopentadiene is 35% *cis* and poly(norbornene) prepared using the residual solution from the polymerization of norbornadiene with OsCl_3 is almost entirely *cis* [43]. Although not effected in this way by chelating monomers, the stereoselectivity of well-defined ruthenium catalysts can also be very sensitive to the type of monomer [35d].

An important distinction can be drawn between the noble metal catalysts, which interact with chelating dienes to produce high *cis* polymers, and the earlier transition metal salts, MoCl_5 , WCl_6 , and TaCl_5 , which exhibit low stereoselectivity with either monoenes or dienes but which become highly *cis* selective [25] in the presence of chelating solvents such as dioxan, the solvent now acting as a bulky spectator ligand at the acidic metal center. The feature each of these catalyst systems has in common is steric crowding at the site, which is believed to promote formation of the less bulky *cis* metallacyclic intermediate and *cis* product; however, stereoselectivity with these modified systems is usually achieved at the expense of reactivity. Another manifestation of this general phenomenon is seen in the ROMP of norbornene using $\text{Ru}(\text{H}_2\text{O})_6(\text{tosylate})_2$ at high pressure in super critical CO_2 [44]. Here, the *cis* content rises from a value of 76% at 2500 psi, to 87% at 4000 psi, to 90% at 5000 psi. The reaction is essentially heterogeneous, but even when methanol is added to achieve homogeneous conditions, a small increase in *cis* content is still observed as the pressure is increased. This is believed to be related to the effect of introducing steric bulk at the site; in all these cases the volume available for metallacycle formation is reduced, leading to the formation of the less bulky *cis* metallacycle.

Subtle effects have been noted in copolymerization studies where different stereoselectivities may be associated with blocks formed from different monomer units in a copolymer. Thus, the c/t ratio of the norbornene and cyclopentene blocks in their copolymers can vary depending on the catalyst system used [45]. For example, RuCl_3 and $\text{MoCl}_5/\text{Me}_4\text{Sn}/\text{Et}_2\text{O}/\text{ethyl acrylate}$ catalyst systems both give medium *cis* cyclopentene sequences, but the norbornene sequences, while 90% *trans* with RuCl_3 , are 75% *cis* with the MoCl_5 -based system. Significantly, the polymers are compositionally blocky, and the high *cis* norbornene sequences in the latter polymer are also c/t blocky. These effects are presumably the result of the different modes of propagation, which depend on the structure of the carbene moiety, which in turn depends on the structure of the last added monomer unit.

Electronic effects at the catalyst site are important in the control of stereoselectivity. A good demonstration of this is the increasing c/t ratio of polymers formed using a series of molybdenum alkylidene complexes (Scheme 3.5-7) in which the degree of fluorination of the alkoxide ligands increases, enhancing the electrophilicity of the metal while steric effects are essentially unchanged; the analogous but less-studied tungsten complexes behave similarly [46]. Table 3.5-1 collects c/t data from a number of polymers formed using the molybdenum series, and, although by no means exhaustive, the data (not always unavailable for the MoF_3 catalyst) illustrate that a fairly systematic increase in c/t ratio is achievable with several monomer types. The degree of control is by no means universal,



Scheme 3.5-7. Series of three well-defined “Schrock-type” molybdenum-based metathesis catalysts with increasing fluorination of the alkoxide ligands.


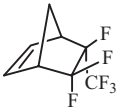
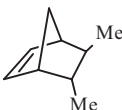
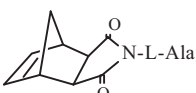


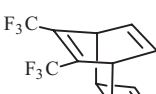
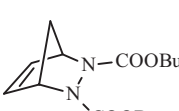
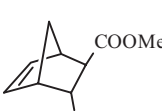
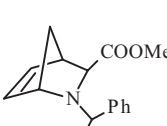
however, and Table 3.5-1 is constructed so as to show a progressive loss of stereo-control over the range of catalysts.

Table 3.5-1 shows that while several poly(norbornene) derivatives can be prepared over a wide range of *c/t* ratios, norbornene and 7-methylnorbornadiene polymerizations are not particularly stereoselective, and with cyclobutene derivatives the results depend very much on the substitution pattern on the ring. The MoF_6 catalyst, which fairly consistently gives high *cis* polymers, can also produce anomalous results, as is seen in the polymerization of benzobarrlene and the disilacyclopentene derivative, where only 30% and 3%, respectively, of the double bonds are *cis*. The products of ROMP reactions of norbornene derivatives are frequently sensitive to the orientation of substituents in the 5 and 6 positions, and here again the *exo* form of the L-alanyl derivative behaves normally with the three catalysts, whereas the *endo* isomer gives the same high *trans* content with each catalyst.


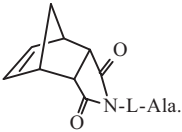

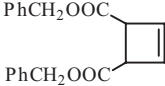
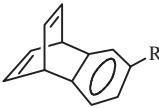



Studies with lower-strain monocyclic rings using these catalysts have shown a trend that is apparently the reverse of that seen with almost all of the more highly strained monomers [2], and a decrease in *c/t* ratio is now found as the degree of fluorination of the catalyst increases. However as the authors point out, secondary metathesis, where the thermodynamic drive is towards a low *c/t* ratio, may contribute to the effect. In this context it is worth noting that even the sterically constrained double bonds in poly(norbornene) can undergo *cis*-to-*trans* isomerism when left in the presence of the highly active tungsten analogue of MoF_6 [46].

The consistent fall in the *c/t* ratio as the ring size increases with a specific catalyst is less ambiguous; because secondary metathesis effects should now be the same for each polymer. The data are presented in graphical form in Figure 3.5-5, and it is noted that after a consistent fall from poly(cyclopentene) to poly(cyclododecene), the *c/t* ratio begins to increase again with poly(cyclododecene). However, it is a matter of speculation whether this is due to stereochemical preferences in the metallacyclobutane intermediate or to the proportion of *trans* isomer in the starting

Tab. 3.5-1. *Cis* double-bond content (%) in ROMP polymers formed using the molybdenum catalysts MoF₀, MoF₃ and MoF₆^a.

Monomer	Catalyst			Reference
	MoF ₀	MoF ₃	MoF ₆	
	2	22	98	6b
	1	<i>b</i>	75	47
	5	44	85	38
	7	43	73	48
	16	<i>b</i>	90	49
	1	<i>b</i>	<i>b</i>	27
	5	<i>b</i>	<i>b</i>	50
	14	66	84	51
	20	54	78	17a
	35	85	98	41

Tab. 3.5-1 (continued)

Monomer	Catalyst			Reference
	MoF ₀	MoF ₃	MoF ₆	
	68	^b	88	30
	10	10	10	48
	48	^b	52	52
	60	^b	90	53
	^a	0	30	54
	^a	^a	3	55
	84	88 ^c	^a	27
	^a	100	^b	56

^a See Scheme 3.5-7 (some of the catalysts have different carbene moiety structure).

^b Data not available.

^c With dimethylphenylphosphine present.

olefin, which increases with ring size and which may have a bearing on the stereochemistry of the product [57].

Despite these monomer-dependent effects, unprecedented degrees of control of c/t ratio and distribution have been observed with these well-defined molybdenum catalysts in certain instances. Figure 3.5-6 demonstrates this for the case of poly(5,6-bis(trifluoromethyl)norbornadiene), where the c/t ratio can be infinitely

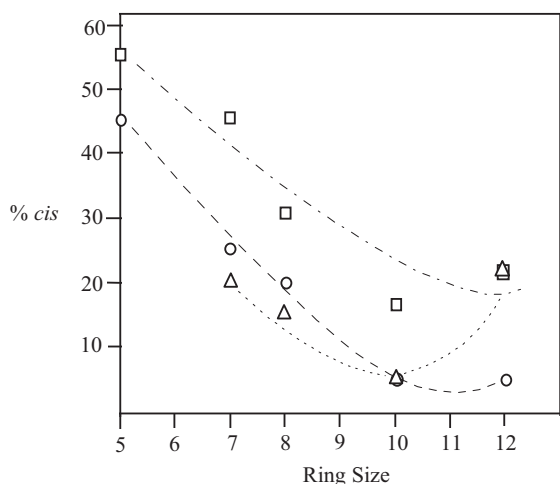


Fig. 3.5-5. The variation of *cis* double-bond content in polyalkenamers formed from a series of monocycloolefins using molybdenum-based catalysts;

□ = $\text{Mo}(\text{CHtBu})(\text{OC}(\text{CH}_3)_3)_2(\text{NAr})$,
 ○ = $\text{Mo}(\text{CHtBu})(\text{OC}(\text{CH}_3)_2\text{CF}_3)_2(\text{NAr})$;
 △ = $\text{Mo}(\text{CHtBu})(\text{OCCH}_3(\text{CF}_3)_2)_2(\text{NAr})$; plot
 was constructed using data taken from [2].

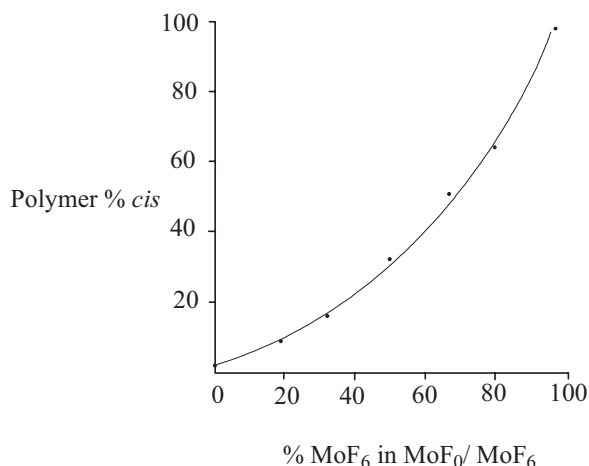
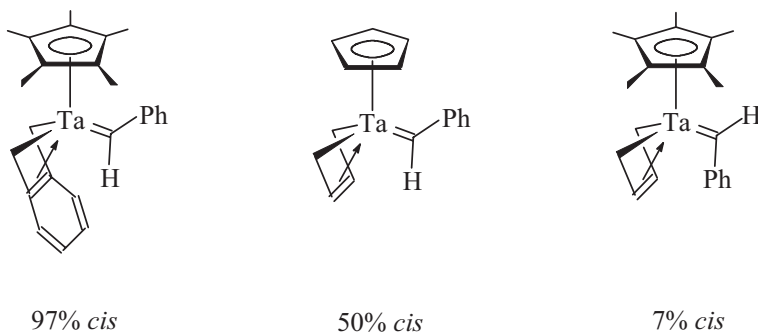


Fig. 3.5-6. Control of the *c/t* ratio in poly(2,3-bis(trifluoromethyl)norbornadiene) achieved by using different proportions of MoF_0 ($\text{Mo}(\text{CHtBu})(\text{NAr})(\text{OC}(\text{CH}_3)_3)_2$) and MoF_6 ($\text{Mo}(\text{CHtBu})(\text{NAr})(\text{OCCH}_3(\text{CF}_3)_2)_2$) as

the catalyst. (*J. Chem. Soc., Chem. Commun.*, W. J. Feast, V. C. Gibson, E. L. Marshall, 1992, 1157–1158, Reproduced by permission of The Royal Society of Chemistry.)

varied merely by adjusting the proportion of the MoF_0 and MoF_6 compounds in the initial reaction mixture, an effect dependent on the rapid exchange of the alkoxide ligands relative to the rate of propagation [58]. Data on the distribution of the *cis* and *trans* double bonds were unfortunately not available for these polymers, but highly *c/t* blocky polymers could be formed by changing the alkoxide ligand *en*



Scheme 3.5-8. Tantalum complexes used for the stereospecific ring-opening metathesis polymerization of norbornene.

route from $-\text{OC}(\text{CH}_3)_3$ to $-\text{OCCH}_3(\text{CF}_3)_2$ [59], the size of the blocks being determined by the relative amounts of monomer and catalyst.

Subtle steric effects and the temperature at which the polymerization is conducted can also be important with these catalyst systems. For example, a change in the alkyl substituents of the imido ligand in MoF_6 from 2,6-diisopropyl to 2-terbutyl results in a decrease in *cis* content from 97% to 78% at ambient temperatures, the effect being most pronounced at elevated temperatures, when the *cis* content falls from 88% to 29%. The *c/t* ratios of polymers formed from a series of such complexes, including those with phenoxy and biphenoxy ligands, all show a substantial fall over a temperature range of -35°C to 65°C [60].

Steric effects are again evident in the polymerization of norbornene using a series of tantalum complexes, and what are believed to be the metathesis-active structures are shown in Scheme 3.5-8. With the Cp^* complexes the *c/t* ratio of the polymer is controlled by the bulk of the diene ligand, with the *o*-xylylene form giving 97% *cis* and the butadiene form giving 7% *cis* poly(norbornene). The steric bulk provided by the Cp^* ligand is important here because the Cp form, at least of the butadiene complex, is essentially non-stereoselective [35c].

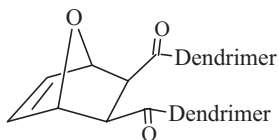
The degree of control of stereoselectivity that is achievable with these early transition metal complexes, primarily by varying the steric and electronic effects of the ligands, has not yet been observed with the ruthenium complexes, which have otherwise had such an impact on the whole metathesis field. Here stereoselectivity is usually lower and, as is the case with their classical antecedents, there is a tendency to form *trans*-biased polymers, even in the polymerization of diene monomers that so profoundly effect the stereoselectivity of the classical ruthenium systems (*vide supra*). Again, the *c/t* ratios of a number of polymers show a fair degree of monomer dependence, as is illustrated by the case of the much-used Grubbs catalyst $\text{RuCl}_2[\text{CHPh}][\text{PCy}_3]_2$, and some interesting comparisons may be made (Scheme 3.5-9). For example, whereas the *exo* isomer of the 7-oxanorbornyl ketal derivative gives high *trans* polymer, the *endo* isomer gives 80% *cis*, which seems to imply involvement of the latter as a spectator ligand, where the ether oxygen atoms and the double bond are in a favorable juxtaposition, reminiscent of the behavior



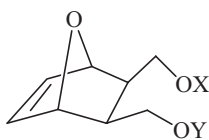
10% [35c]



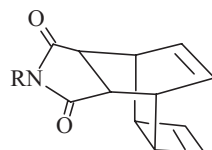
14% [35d]



24% [61]



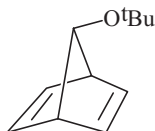
50% [63]



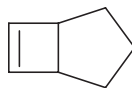
75% [66]



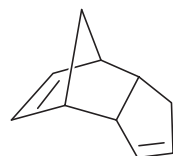
17% [35d]



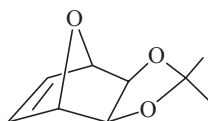
29% [35d]



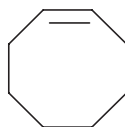
58% [64]



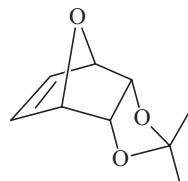
13% [35d]



30% [62]



62% [65]



80% [62]



19% [35d]

Scheme 3.5-9. Variation of *cis* double-bond contents in polymers formed from a range of monomers using the Grubbs catalyst $\text{RuCl}_2(\text{CHPh})(\text{PCy}_3)_2$.

of RuCl_3 with diene monomers. Another comparison is that between the polymers formed from cyclopentene and cyclooctene, where the latter is substantially higher *cis*, apparently the reverse of the effect seen with molybdenum-based systems (Figure 3.5-5). Yet, in a recent study in this area using the second-generation Grubbs catalyst, $\text{RuCl}_2(1,3\text{-dimesityl-4,5-dihydroimidazol-2-ylidene})(\text{PCy}_3)_2$, poly(cyclopentene) had a *cis* content of 50%, while poly(cyclooctene) had a *cis* con-

tent of only 15% [67]. The stereochemistry of polymers formed from the lower-strain monocyclic olefins is clearly very difficult to predict.

ROMP of cyclobutene compounds, for example bicyclo[3.2.0]hept-1-ene (Scheme 3.5-9), also results in low stereoselectivity, as it does with RuCl_3 , which is essentially non-stereoselective with this monomer [68]; often there is less stereoselectivity with more highly strained monomers. Catalysts based on the $[\text{RuCl}_2(\text{arene})]_2$ /trimethylsilyldiazomethane system are uniquely high *trans*-directing with a variety of norbornadiene derivatives, but even here the behavior becomes less stereoselective as the bulk of the monomer substituents increases, an effect also produced by the addition of PCy_3 to the catalyst [69].

As with the molybdenum-based complexes, but to a lesser extent, the effect of increasing the electron-withdrawing ability of ligands both with classical [57, 70] and well-defined [71] ruthenium-based systems, substituting trifluoroacetate for acetate, is to increase both the *c/t* ratio and catalyst activity.

The interpretation of *cis* and *trans* stereoselectivity, in metathesis reactions in general, has excited the interest of numerous groups of workers since the early 1970s and continues unabated with the advent of well-defined catalysts that have the ability to produce both high enantiomeric excess, from reactions of acyclic substrates, and highly stereoregular ROMP polymers.

Originally, the relative energies of the metallacarbene-olefin complex and the metallacyclobutane were invoked to explain a perceived lack of stereoselectivity in ROMP, compared to acyclic metathesis, with a range of active catalysts. However, it became clear that highly active ROMP catalysts could also be highly stereoselective, and, in addition, detailed ^{13}C NMR studies of poly(norbornadiene) and poly(cyclopentene) revealed the important fact that the distribution of double bonds in polymers, when the *cis* content was greater than ~ 0.4 , was decidedly blocky (Figure 3.5-7 and Section 3.5.3.1) [72]. This work, supported by the analysis of polymers formed from a wider range of catalysts [73, 74], led to the important concept that the stereochemical outcome of a given propagation event was to some extent determined by the stereochemistry of the previous event. These studies, and more recent work that considers the possibility of propagation via isomeric forms of well-defined molybdenum complexes [60], have shifted the emphasis from the metallacyclobutane as the species that regulates stereoselectivity to the metallacarbene, although the latter species may well be important in determining the stereochemistry of polymers formed from lower strain monomers (*vide supra*).

The different forms of the metallacarbene, with a vacant site for monomer coordination and distinguished by the stereochemistry of the last-formed double bond, were designated P_c , P_t , and P (Scheme 3.5-10) and proposed as propagating species. It was believed that the last-formed double bond, if not formally coordinated to the metal center, was at least in its vicinity when the next monomer unit approached. When the last-formed double bond was *cis*, the resulting P_c could react with monomer, but only when it was in a *cis* orientation, thus determining the stereochemistry of the next monomer insertion and leading to a sequence of *cis* double bonds. P_t , believed to be inaccessible to monomer in any orientation, required relaxation to an open-structure P , where the orientation of monomer

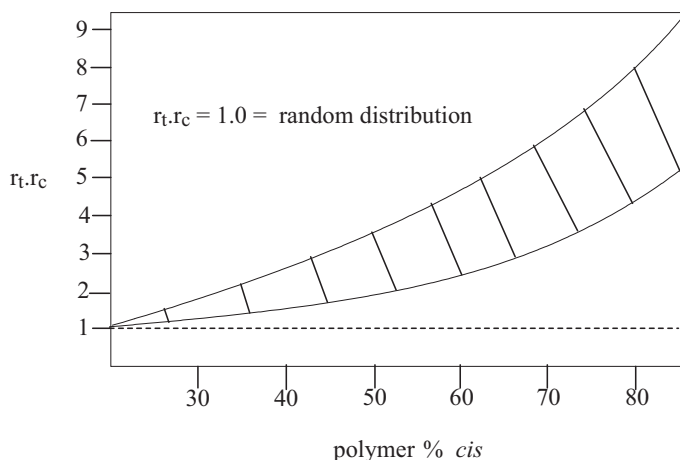
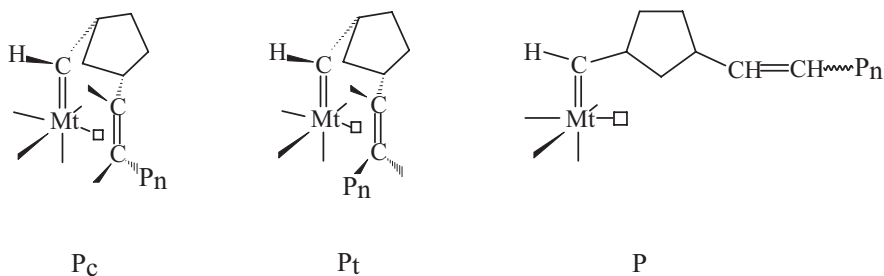


Fig. 3.5-7. Increasingly blocky distribution of *cis* and *trans* double bonds with increasing *cis* double bond content for a range of poly(norbornene)s. (Reprinted from *Ring-Opening Metathesis Polymerization and Related Chemistry*; NATO Science series II: *Mathe-*

matics, Physics and Chemistry – Vol. 56, V. Emir-Ebrahimi, J. G. Hamilton, J. J. Rooney, *Blockiness and Tacticity in Metathesis Polymers*, Copyright 2002, with permission from Kluwer Academic Publishers, Amsterdam).



Scheme 3.5-10. Species believed to be involved in the ROMP of norbornene showing the different locations of the last-formed double bond. □ represents the vacant ligand position.

addition was controlled by other factors, such as the nature of the ligands attached to the metal or the stability of the *cis* or *trans* metallacycles, often leading to *trans* sequences. Thus, the *cis* after *cis* and *trans* after *trans* feature found in higher *cis* ROMP polymers and the *cis* from *cis* and *trans* from *trans* feature in the metathesis of many acyclics could be rationalized [57]. Although these aspects of polymer stereochemistry have received much less attention in polymers formed from the well-defined systems, preliminary results show that these ideas might be important in these cases also. For example, the molybdenum complex, MoF₀, gives a c/t blocky poly(norbornene) [52] (*vide infra*), while the ruthenium-based examples give almost random polymers [52], even when these are moderately high *cis*, as is the case with the second-generation Grubbs catalyst [65].

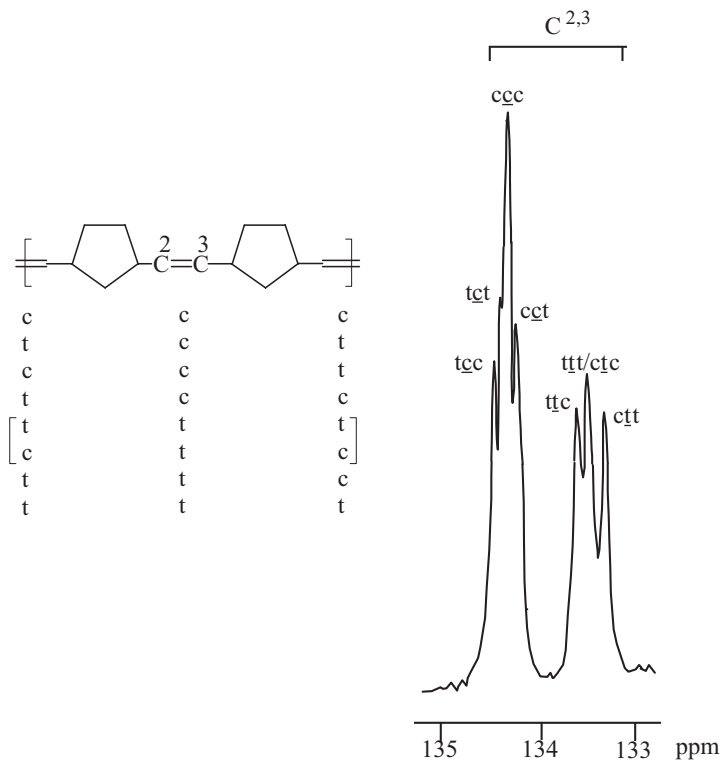
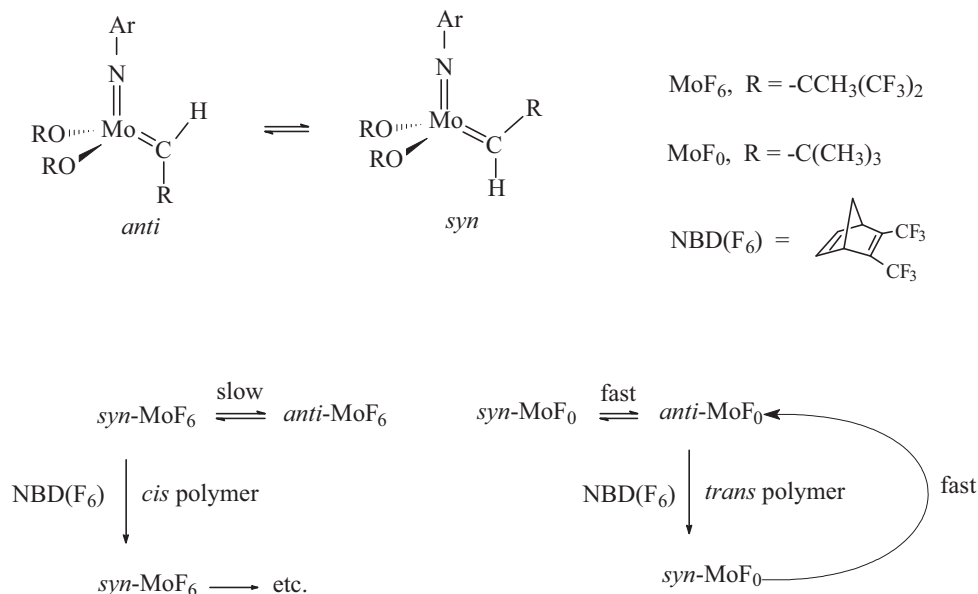


Fig. 3.5-8. Double-bond triad structures in poly(norbornene) and their ^{13}C NMR signals in the spectrum of an approximately 50% *cis* sample of the polymer.

A further refinement of these mechanistic proposals was suggested when the ^{13}C NMR spectra of poly(norbornene) samples, with a range of c/t ratios, revealed additional fine structure in the olefinic region of their spectra, which was attributed to double-bond triad structures (Figure 3.5-8). In certain polymers with a moderate to high *cis* content, the central signal of the *trans* group, which represents a *trans* double bond flanked by *trans* double bonds, $\text{t}\underline{\text{t}}\text{t}$, superimposed on *trans* flanked by *cis*, $\text{c}\underline{\text{t}}\text{c}$, was frequently of much lower intensity than predicted when compared to the $\text{t}\underline{\text{t}}\text{c}$ and $\text{c}\underline{\text{t}}\text{t}$ triads (Figure 3.5-8). This implied that the *trans* double bonds in the polymers had a strong tendency to occur in pairs rather than singly or in groups; with other high *cis* polymers, the central feature dominated, indicating the existence of t_n blocks. These features, analogous to error repair and error propagation, respectively, in isotactic poly(propylene) formation [75], were taken as evidence for the involvement of the penultimate double bond, necessitating the subdivision of the P_t species into P_{tt} and P_{ct} .

It is generally acknowledged that with the classical catalyst systems, used in all the studies described above, the actual working catalyst is never observed. Therefore, the mechanistic proposals are based solely on a detailed analysis of the



Scheme 3.5-11. *Syn* and *anti* rotamers of molybdenum-based carbene complexes and the mechanism of formation of high *cis* and high *trans* poly(2,3-bis(trifluoromethyl)norbornadiene).

microstructure of polymers; the polymer thus was viewed as a virtual recording of events that had occurred at the catalyst site. Now, with the well-defined initiators in several cases, the metallocarbene and metallacyclic intermediates have been identified spectroscopically and the progress of some reactions may thus be followed [1b], although any mechanistic proposals arising must still be consistent with the microstructure of the polymer as determined by ¹³C NMR analysis.

Much of this work has been carried out with the molybdenum complexes, which are well suited to these studies because there is no pre-equilibrium or catalyst activation step before the formation of the actual chain carrier. The interaction with a substrate molecule can thus be studied directly using ¹H NMR techniques, although the propagating species has also been observed in reactions with the ruthenium-based systems [32, 76]. In any event, the success of such experiments depends largely on the relative rates of initiation and propagation.

As mentioned above, the c/t ratio of polymers formed using molybdenum complexes of the type Mo(NAr)(CHR)(OR')₂ (Scheme 3.5-7) was found to be highly dependent on the electron-withdrawing ability of the alkoxide ligands and also on the type of monomer. With these well-defined molybdenum systems, the concept of the involvement of distinct metallocarbene species, now *syn* and *anti* rotamers, has again been invoked to explain the observed stereoselectivities [60] (Scheme 3.5-11). These rotamers are endowed with certain properties. They are in equilibrium and interconvert at a rate that depends sensitively on the type of ligand, and they have very different reactivities, with the *anti* being much more

reactive than *syn*: upon reaction with monomer, the *syn* rotamer gives a *cis* double bond and another *syn* rotamer, while the *anti* gives a *trans* double bond and also yields a *syn* rotamer. An example of their proposed mode of action is provided by the polymers formed from 2,3-bis(trifluoromethyl)-norbornadiene using the MoF₆ and MoF₀ compounds (Scheme 3.5-11). With the MoF₆ compound, propagation occurs via the *syn* rotamer, which in turn yields another *syn* rotamer and the almost exclusive formation of *cis* sequences. With the MoF₀ catalyst, high *trans* polymer is formed at the more reactive *anti* rotamer, yielding a *syn* rotamer that, even though it could react with monomer to give a *cis* unit, reverts to the *anti* form faster than monomer can react with it. The existence of such equilibria is further demonstrated by the case of the very slow polymerization of the highly sterically hindered 1,7,7-trimethylnorbornene using the MoF₆ catalyst [77]. A high *trans* polymer is now formed almost exclusively with the *anti* rotamer because this monomer can-

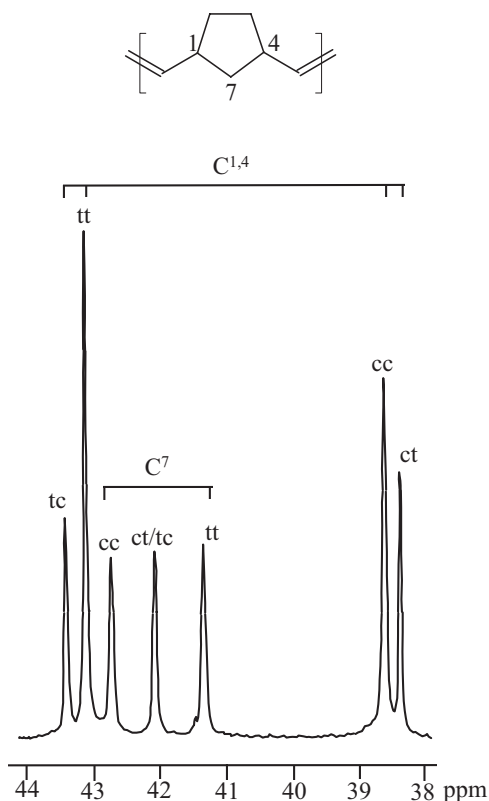


Fig. 3.5-9. C⁷ and C^{1,4} region in the ¹³C NMR spectrum of the 48% *cis* poly(norbornene) with a blocky *c/t* distribution prepared using the MoF₀ catalyst. A *c/t* random polymer with this *c/t* ratio would have a 1:2:1 peak intensity ratio for the C⁷ *tt*:*ct/tc*:*cc*.

not react with the *syn* rotamer for steric reasons; the rate of polymerization is now controlled by the rate of *syn*-to-*anti* conversion.

Further work will be required on the detailed microstructures of polymers formed with these catalysts because, as mentioned above, preliminary work [52, 65] shows that the 48% *cis* poly(norbornene) produced using the MoF₀ catalyst is in fact c/t blocky (Figure 3.5-9), and it is difficult to see how this could arise simply by propagation through the *syn* and *anti* forms described above, raising the possibility that the last-formed double bond is involved in some way in the propagation reaction with these well-defined catalysts.

3.5.4.2

Tacticity

A fair measure of success has been achieved in identifying catalyst structural parameters and reaction conditions that control the c/t ratio of ROMP polymers, but the factors that determine whether or not a polymer will be tactic, let alone whether it will be syndiotactic or isotactic, are less well established. Nevertheless a number of examples of tactic ROMP polymers, formed using the classical [1b] as well as the well-defined systems (Table 3.5-2), have been reported.

Very high *cis* polymers have been formed from 1-methylnorbornene using a tungsten-aryloxy carbene complex [24] (Scheme 3.5-12). They are also totally regioregular and quite syndiotactic and as such must be formed at sites that alternate between (+) and (−) chiral forms as a result of monomer insertion, with a reasonable degree of regularity, in successive propagation cycles. Such catalysts could conceivably be prepared with modified ligands that would offer the opportunity to tune the site, sterically and electronically, and thereby help to delineate the factors that are important in this type of control. Earlier studies revealed that it was possible to form what was the first example of an essentially perfectly alternating copolymer of the two enantiomers of 1-methylnorbornene by using the classical ReCl₅ catalyst [78].

A good demonstration of how the ligands can influence stereoselectivity at a ROMP catalyst site is seen with a series of molybdenum complexes, MoF₆ and two others with increasing fluorination of the alkoxide ligands, in the polymerization of 2,3-bis(trifluoromethyl)-norbornadiene [60]. The tacticity changes from moderately isotactic to quite highly syndiotactic. Interestingly, essentially no change in tacticity is observed when the monomer changes to the bis-carboxymethyl derivative.

An example of the influence of chiral ligands is provided by a molybdenum binaphtholate catalyst (Scheme 3.5-12), which is also available as the (+) enantiomer [79]. Polymerization of (+)-5,6-(dimethoxymethyl)norbornene using the racemic catalyst gave a polymer with a distinctly bimodal GPC trace (Figure 3.5-10a), which arises because of the different rates of formation of two isotactic polymer chains at the (+) and (−) catalyst sites.

The lower peak intensity and the lower molecular weight of one of the peaks is consistent with slower polymer formation when the (+)-monomer reacts at the “wrong” catalyst site; a predictable unimodal GPC (Figure 3.5-10b) was obtained

Tab. 3.5-2. Qualitative tacticity of various polymers prepared with different well-defined catalysts.

Catalyst ^a	Monomer ^b	% <i>cis</i>	<i>c/r</i>	<i>c/m</i>	<i>t/r</i>	<i>t/m</i>	Reference
W(aryloxy)	1-MNBE	100	✓				24
MoF ₀	7-MNBE	68	✓			✓	30
MoF ₆	"	88	— ^c	—	—	—	30
Ru(P) ₂	"	29	✓		✓		30, 35c
Ru(NHC) ₂	"	48	✓		—	—	35e
Ru(P)(NHC')	"	53	✓		—	—	35e
MoF ₆	(+)-5,6-DMNBE	85		✓	—	—	38
MoF ₃	"	58		✓	—	—	38
MoF ₀	"	5		✓	—	—	38
Mo(BINO)	menthNBD	99		✓			17a
MoF ₉	"	99		✓			17a
MoF ₀	"	6			✓		17a
MoF ₆	2,3-DMNBD	98		✓			60
MoF ₆	2,3-DBNBD	99		✓			60
Ru(P) ₂	7-MNBE	20		✓		✓	35c
Ru(NHC) ₂	"	34		✓	✓		35e
Ru(P)(NHC')	"	44		✓	✓		35e
Ru(dtbpm)(OTf) ₂	"	8		✓	✓		35a
Ru(dtbpm)(OTf) ₂	7-MNBD	8	—	—	✓		35a
Ru(dtbpm)(BArF) ₂	"	10	—	—	—	—	35a

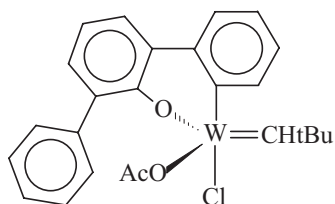
^a Catalyst code: MoF₀, MoF₃, MoF₆ as in Scheme 3.5-6 (MoF₉, alkoxy ligand is OC(CF₃)₃); W(aryloxy) = WCl(CHC(CH₃)₃)(2,6-C₆H₃Ph₂)(aryloxy)(OEt₂); Mo(BINO) = Mo(CMe₂Ph)(N-2,6-diisopropylphenyl)[(±)-BINO(SiMe₂Ph)₂]; Ru(P)₂ = RuCl₂(CHPh)(PCy₃)₂; Ru(NHC)₂ = RuCl₂(CHPh)(1,3-dicyclohexylimidazol-2-ylidene)₂; Ru(P)(NHC') = RuCl₂(CHPh)(PCy₃)(1,3-(+)-1-phenylethylimidazol-2-ylidene); Ru(dtbpm)(OTf)₂ = [(bis(di-ter-butylphosphino)methane-κ²P)ClRuCHCHC(CH₃)₂]₂(O₃SCF₃)₂; Ru(dtbpm)(BArF)₂ = [(bis(di-ter-butylphosphino)methane-κ²P)ClRuCHCHC(CH₃)₂]₂(B(3,5-CF₃)₂C₆H₃)₄)₂.

^b Monomer code: (+)-5,6-DMNBE = (+)-endo,exo-5,6-dimethylnorbornene; 1-MNBE = 1-methylnorbornene; 7-MNBD = 7-methylnorbornadiene; menthNBD = 2,3-bis((menthoxy)carbonyl)-norbornadiene; 2,3-DMNBD = 2,3-bis(methylcarboxy)-norbornadiene; 2,3-DBNBD = 2,3-bis(ter-butylcarboxy)norbornadiene; 7-MNBE = anti-7-methylnorbornene.

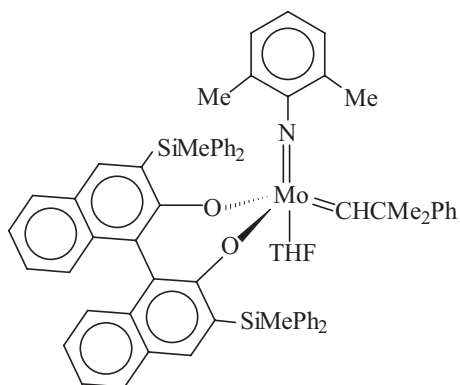
^c — = *trans* or *cis* junctions have equal proportions of *m* and *r* dyads.

when a single enantiomer of the catalyst was used. When using different solvents or different substituents in the binaphtholate ligands of these complexes, the difference between the two distributions is seen to vary, demonstrating the potential of such catalysts to achieve much higher enantioselection in ROMP reactions.

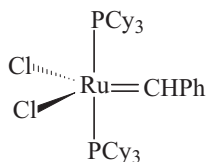
Despite the fact that the high *trans* polymers formed by using the classical RuCl₃ catalyst have all proved to be atactic, whenever this could be determined, the neutral ruthenium carbene complex of Grubbs [35d] and the *N*-heterocyclic carbene variety of Herrmann [35f] (see Scheme 3.5-12) both produce moderately tactic



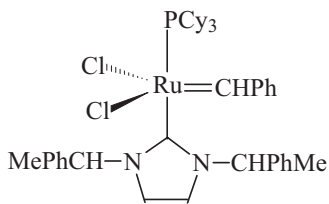
Basset [24]



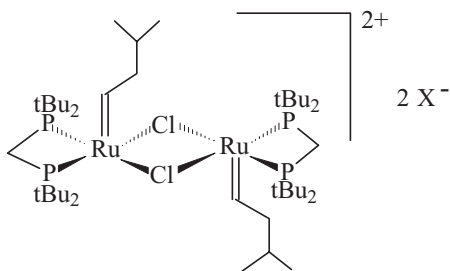
Schrock [79]



Grubbs [35c]



Herrmann [35e]



Hofmann [35a, 35b]

Scheme 3.5-12. Examples of well-defined catalysts used in the production of ROMP polymers with varying degrees of stereoregularity.

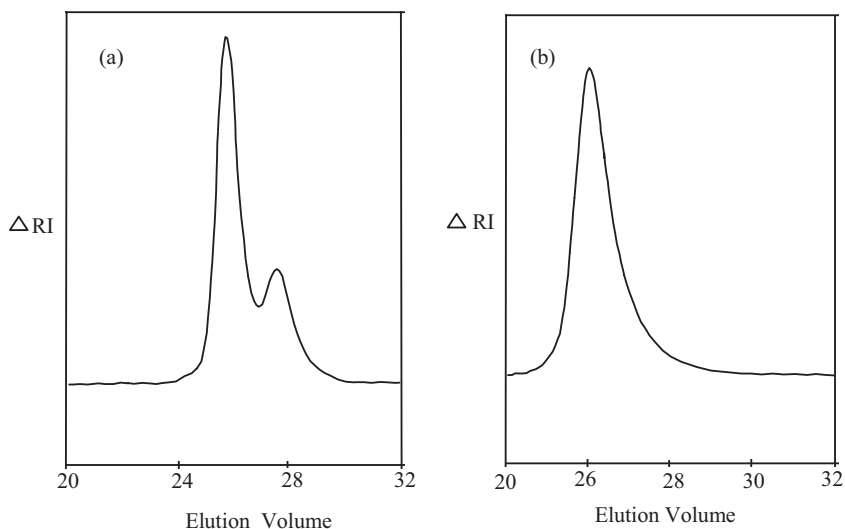


Fig. 3.5-10. GPC traces of poly((+)-5,6-dimethoxymethylnorbornene) prepared using (a) the racemic form of a chiral molybdenum-based catalyst and (b) a single enantiomer of the same catalyst.

polymers from 7-methylnorbornene. Although the *cis* junctions in these predominantly *trans* polymers have an isotactic bias, the tacticity of the *trans* junctions switches from strongly isotactic in the former catalyst to strongly syndiotactic in the latter. Although one assumes that different permanent ligands may be present in the actual propagating species formed from these two complexes (PCy_3 and *N*-heterocyclic carbene), it is not obvious why such a change should produce these different tacticities. As was noted above in the context of *c/t* ratios, the tacticity is also monomer dependent, and a different tacticity profile is observed when 7-methylnorbornadiene is the monomer [35f].

Another more recent, and perhaps more easily rationalized, example of how catalyst structural factors control tacticity has been provided by a ^{13}C NMR study of a series of polymers, prepared from 7-methylnorbornadiene, using novel cationic ruthenium complexes with different counterions (Scheme 3.5-12) [35a, 35b]. Each polymer was characteristically high *trans* but had significant differences in the proportions of *r* and *m* structures associated with the *trans* units, as can be seen in their ^{13}C NMR spectra (Figure 3.5-11). The catalysts bearing the small, hard triflate anion yielded highly syndiotactic polymers (Figure 3.5-11a), whereas the same complex with the much more bulky $\text{B}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$ anion had equal proportions of syndiotactic and isotactic junctions (Figure 3.5-11b). Each of the polymers had a very blocky distribution of *m* and *r* units, despite the fact that the latter was, in one sense, atactic, in that it contained equal proportions of *m* and *r* units. A counterion effect has been noted with other ruthenium catalysts [80] in the context of polymer *c/t* ratios; here, although the *c/t* ratio is not effected by the dif-

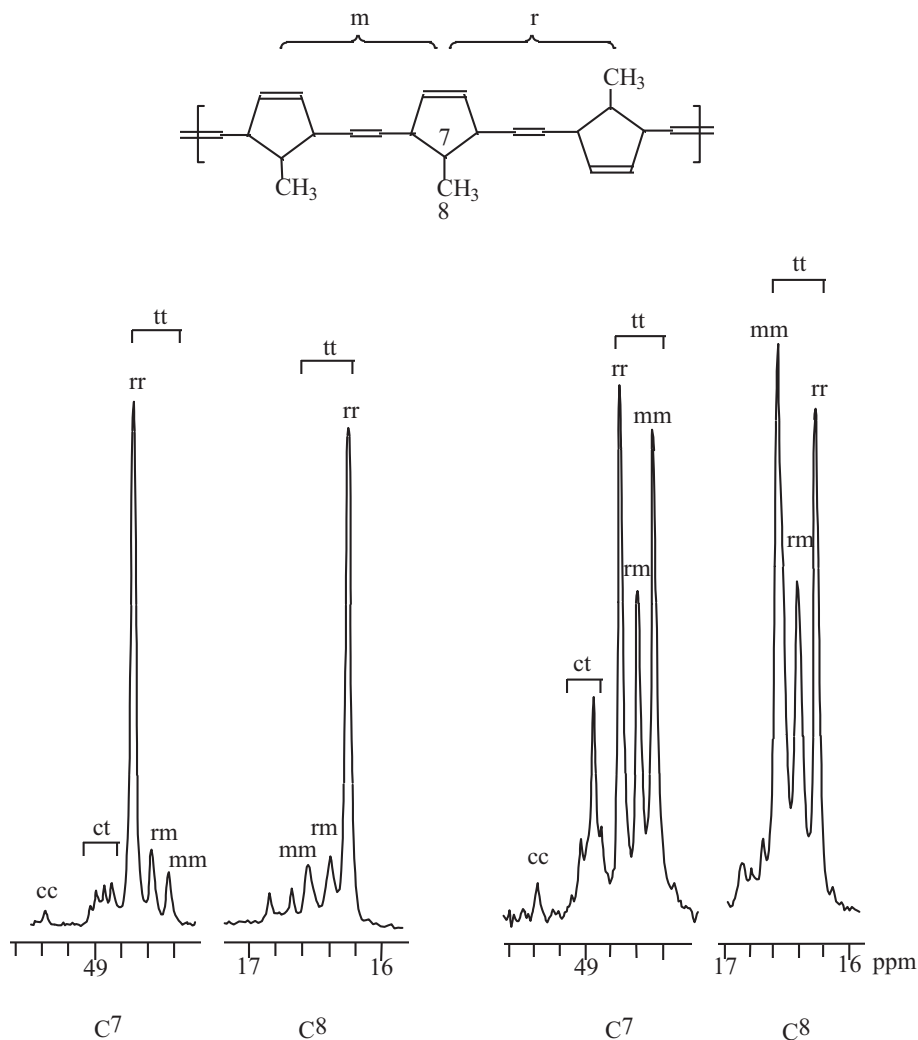


Fig. 3.5-11. ^{13}C NMR spectra of polymers formed from 7-methylnorbornadiene using the ruthenium-based cationic catalysts [(bis(diter-butylphosphino)methane-

$\kappa^2\text{P})\text{ClRuCHCHC}(\text{CH}_3)_2)_2\text{X}^-$, C7 and C8 regions, (a) highly syndiotactic polymer, X = (O_3SCF_3) and (b) atactic polymer, X = $(\text{B}(3,5\text{-CF}_3)_2\text{C}_6\text{H}_3)_4$.

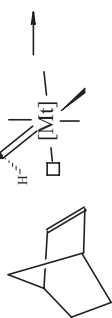
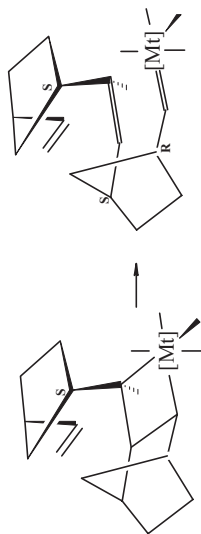
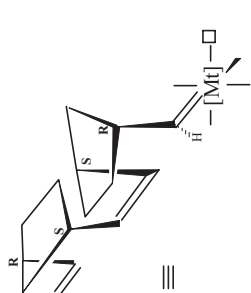
ferent counterion, the proximity of the more strongly coordinating triflate anion to the site is believed to be responsible for maintaining a particular site geometry through successive propagation cycles [81]. It is significant and interesting that the strength of cation-anion interactions is believed to be important in the production of highly tactic poly(propylene) using cationic metallaocene catalysts [81].

A natural progression would be to use such ruthenium-based complexes with chiral ligands. These have been developed recently and have been successful in directing stereochemistry in acyclic metathesis, but as yet there is no information on their behavior in ROMP reactions [82].

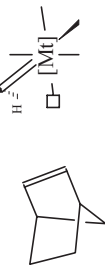
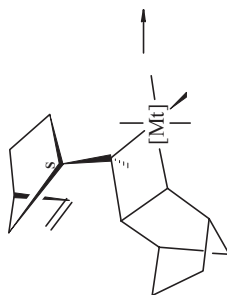
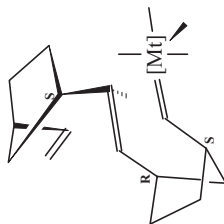
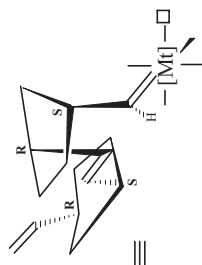
The first attempt to rationalize ROMP polymer tacticity was based on an analysis of polymers formed from optically active monomers (which allow unambiguous determination of tacticity, Section 3.5.3.2) using the classical catalyst systems. This work showed that the *m* or *r* tacticity of a given dyad unit was related to the stereochemistry of the double bond in that unit; *cis* junctions had a tendency to be syndiotactic, and *trans* junctions were either isotactic or atactic [37]. By virtue of this fact, a polymer was still considered to be tactic even though, overall, it may have had syndiotactic and isotactic units in any proportion. These considerations, combined with the fact that high *cis* polymers frequently had a blocky distribution of double bonds (Section 3.5.4.1), were consistent with a propagation reaction involving the kinetically distinct metallocarbenes, P_c , P_t and P , (Scheme 3.5-10) with pseudo-octahedral geometry and a vacancy to accommodate the complexation at the *exo* face of a monomer molecule. These sites were chiral by virtue of the orientation of the carbene ligand, with respect to the vacancy, and Scheme 3.5-13 depicts the basic features of this mechanism for norbornene-type monomers. With this model, *cis* double-bond formation gives syndiotactic dyads and *trans* double bonds give isotactic dyads; atactic junctions are formed preferentially at *P*-type sites, where there is no last-formed double bond involvement or when epimerization of the site is faster than propagation or if relaxation to a symmetrical form occurs. Although a degree of chain-end control could not be ruled out entirely, this enantiomorphic site model was favored because it accommodated the tacticity preference expressed at *cis* and *trans* double bonds in many different polymers [37].

More recently, tacticity data of ROMP polymers formed using the well-defined initiators have been accumulating, and although in a number of cases the *cis*/syndiotactic and *trans*/isotactic relationship, observed with the classical systems, is still apparent, there are many other polymers where it does not hold, as can be seen in Table 3.5-2. It is interesting that until the advent of these initiators there were no examples of polymers with predominantly *cis* isotactic or *trans* syndiotactic stereochemistry, but this seeming inconsistency may have its origins in the different physical states in which the two classes of catalyst are likely to exist. Many of the multi-component and single-salt classical systems are clearly heterogeneous in nature [83], whereas the well-defined systems are truly homogeneous. Therefore, in the former systems, reactions may be taking place at the surface of suspended solids, which in itself may have an important role to play in determining tacticity by restricting the mode of approach of the monomer molecule or by helping to maintain a particular site geometry. Homogeneous systems would not be subject to the same restrictions, and the monomer would have access to the different faces of a catalyst site, leading to a wider range of polymer tacticities. Analogous phase-dependent differences in tacticity have been noted in the polymerization of α -olefins with Ziegler-Natta catalysts [84].

A modified mechanism, based on that outlined in Scheme 3.5-13 but that ac-



Cis syndiotactic: Site stereochemistry alternating



Trans isotactic: Site stereochemistry maintained

Scheme 3.5-13. Formation of *cis*, syndiotactic and *trans*, isotactic junctions in poly(norbornene) at an octahedral catalyst site with a vacancy (\square) for monomer coordination.

commodates a wider range of polymer tacticities, has been suggested [35f]. The basic idea still incorporates the concept of propagation using kinetically distinct metallocarbenes, P_c and P_t , but now both these species can be chain carriers and can react with monomer at either face so that the formation of every type of dyad unit is accommodated while still allowing for a blocky distribution of double bonds. There may be a preferential direction of attack with one of these species, but not the other, allowing for the fact that tacticity of *cis* junctions can remain constant, while the tacticity of *trans* junctions can reverse, as seen with the ruthenium-based catalysts discussed above. Alternatively, one species may not react at all until the double bond has departed, leading to another chiral species, P , that in turn may relax to a symmetrical species P' and the formation of both atactic *cis* and *trans* junctions. Use of species such as P_c and P_t , where the previously inserted monomer is so intimately associated with the catalyst site, also helps to explain the dependence of tacticity on monomer type.

Despite the fact that many years have elapsed since ROMP polymer tacticity was identified and analyzed, the advent of the second-generation catalysts means that there is scope for further studies in this area before the full potential of the reaction is realized.

References

- (a) A. H. FAWCETT, J. G. HAMILTON, J. J. ROONEY in *Polymer Spectroscopy*, Ed. A. H. FAWCETT, John Wiley & Sons Chichester, 1996, (b) K. J. IVIN, J. C. MOL, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, London, 1997; (c) J. G. HAMILTON, *Polymer* **1998**, 39, 1669, (d) V. DRAGUTAN, R. STRECK, *Studies in Surface Science and Catalysis*, Vol. 131, Catalytic Polymerization of Cyclic Olefins, Elsevier, Amsterdam, 2000, (e) *Ring-Opening Metathesis Polymerization and Related Chemistry*, NATO Science series II: Mathematics, Physics and Chemistry – Vol. 56, Kluwer Academic Publishers, Amsterdam, 2002.
- P. DOUNIS, W. J. FEAST, A. M. KENWRIGHT, *Polymer* **1995**, 36, 2787–2796.
- E. A. OFSTEAD, *Encyclopedia of Polymer Science and Engineering*, Vol. 11, John Wiley & Sons, New York, 1988.
- F. HAAS, D. THEISEN, *Kautsch. Gummi, Kunstst.*, **1970**, 23, 502.
- G. DALL'ASTA, P. MENEGHINI, U. GENARO, *Makromol. Chem.*, **1972**, 154, 279–290.
- (a) W. W. YAU, J. J. KIRKLAND, D. D. BLY, *Modern Size-Exclusion Liquid Chromatography*, John Wiley & Sons, New York, 1979, (b) J. H. OSKAM, R. R. SCHROCK, *J. Am. Chem. Soc.*, **1993**, 115, 11831–11845.
- (a) J. H. EDWARDS, W. J. FEAST, D. C. BOTT, *Polymer*, **1984**, 25, 395–398, (b) L. Y. PARK, R. R. SCHROCK, S. G. STIEGLITZ, W. E. CROWE, *Macromolecules*, **1991**, 24, 3489–3495.
- Y. V. KORSHAK, V. V. KORSHAK, G. KANISHKA, H. HOCKER, *Makromol. Chem., Rapid Commun.*, **1985**, 6, 685–692.
- F. L. KLAFFETTER, R. H. GRUBBS, *Synthetic Metals*, **1989**, 28, D105.
- C. B. GORMAN, E. J. GINSBURG, R. H. GRUBBS, *J. Am. Chem. Soc.*, **1993**, 115, 1397–1409.
- V. AMIR-EBRAHIMI, D. BYRNE, J. G. HAMILTON, J. J. ROONEY, *Makromol. Chem. Phys.*, **1995**, 196, 327–342.
- M. W. WAGAMAN, R. H. GRUBBS, *Macromolecules*, **1997**, 30, 3978–3985.
- Y. P. YAMPOLSKII, E. S. FINKELSHTEIN, K. L. MAKOVETSKII, V. I. BONDAR, V. P. SHANTAROVICH, *J. Appl. Polym. Sci.*, **1996**, 62, 349–357.

- 14 (a) M. UNGERANK, B. WINKLER, E. EDER, F. STELZER, *Macromol. Chem.*, **1997**, 198, 1391–1410, (b) L. NOIREZ, M. UNGERANK, F. STELZER, *Macromolecules*, **2001**, 34, 7885–7893.
- 15 (a) T. STEINHAUSLER, F. STELZER, E. ZENKL, *Polymer*, **1994**, 35, 616–621, (b) S. C. G. BIAGINI, R. G. DAVIES, V. C. GIBSON, *Chem. Commun.*, **1999**, 235–236.
- 16 T. C. CHUNG, S. RAMAKRISHNAN, M. W. KIM, *Macromolecules*, **1991**, 24, 2675–2681.
- 17 (a) R. O'DELL, D. H. MCCONVILLE, G. E. HOFMEISTER, R. R. SCHROCK, *J. Am. Chem. Soc.*, **1994**, 116, 3414–3423, (b) M. KANAI, K. H. MORTELL, L. KIESSLING, *J. Am. Chem. Soc.*, **1997**, 119, 9931–9932, (c) J. A. SATTIGERI, C.-W. SHIAU, C. C. HSU, F.-F. YEH, S. LIOU, B.-W. JIN, T.-Y. LUH, *J. Am. Chem. Soc.*, **1999**, 121, 1607–1608, (d) D. M. WATKINS, M. A. FOX, *Macromolecules*, **1995**, 28, 4939–4950.
- 18 G. H. BEAVEN, E. A. JOHNSTON, R. G. J. MILLER, H. A. WILLIS, *Molecular Spectroscopy*, Heywood & Co., Ltd., London, 1961.
- 19 B. DE CLERCQ, T. SMELLINCKX, C. HUGELIER, N. MAES, F. VERPOORT, *Appl. Spectrosc.*, **2001**, 55, 1564–1567.
- 20 D. FU, L.-T. WENG, B. DU, O. K. C. TSUI, B. XU, *Adv. Mater.*, **2002**, 14, 339–343.
- 21 J. G. HAMILTON, K. J. IVIN, J. J. ROONEY, *J. Mol. Catal.*, **1985**, 28, 255–278.
- 22 H. T. HO, K. J. IVIN, J. J. ROONEY, *Makromol. Chem.*, **1982**, 183, 1629–1646.
- 23 J. G. HAMILTON, K. J. IVIN, J. J. ROONEY, *Brit. Polym. J.*, **1984**, 16, 21–33.
- 24 J.-M. BASSET, M. LECONTE, F. LEFEBVRE, J. G. HAMILTON, J. J. ROONEY, *Macromol. Chem. Phys.*, **1997**, 198, 3499–3506.
- 25 B. AL-SAMAK, V. AMIR-EBRAHIMI, D. G. CORRY, J. G. HAMILTON, S. RIGBY, J. J. ROONEY, J. M. THOMPSON, *J. Mol. Catal. A: Chemical*, **2000**, 160, 13–21.
- 26 A. M. KENWRIGHT in reference [1e], page 57.
- 27 Z. WU, R. H. GRUBBS, *Macromolecules*, **1995**, 28, 3502–3508.
- 28 B. AL-SAMAK, V. AMIR-EBRAHIMI, A. G. CARVILL, J. G. HAMILTON, J. J. ROONEY, *Polymer Inter.* **1996**, 41, 85–92.
- 29 A. G. CARVILL, R. M. E. GREENE, J. G. HAMILTON, K. J. IVIN, A. M. KENWRIGHT, J. J. ROONEY, *Macromol. Chem. Phys.*, **1998**, 199, 687–693.
- 30 K. J. IVIN, A. M. KENWRIGHT, E. KHOSRAVI, J. G. HAMILTON, *J. Organomet. Chem.*, **2000**, 606, 37–48.
- 31 J. G. HAMILTON, K. J. IVIN, J. J. ROONEY, *Brit. Polym. J.*, **1988**, 20, 91–95.
- 32 N. SEEHOF, W. RISSE, *Macromolecules*, **1993**, 26, 5971–5975.
- 33 J. G. HAMILTON, J. J. ROONEY, D. G. SNOWDEN, *Makromol. Chem.*, **1993**, 194, 2907–2922.
- 34 V. AMIR-EBRAHIMI, D. A. K. CORRY, J. G. HAMILTON, J. J. ROONEY, *J. Mol. Catal.*, **1998**, 133, 115–122.
- 35 (a) S. M. HANSEN, M. A. O. VOLLAND, F. ROMINGER, F. EISENTRAGER, P. HOFMANN, *Angew. Chem., Int. Ed.*, **1999**, 38, 1273–1276. (b) J. G. HAMILTON, P. HOFMANN, J. J. ROONEY, M. A. O. VOLLAND, to be published (c) K. MASHIMA, M. KAIIDZU, Y. TANAKA, Y. NAKAYAMA, A. NAKAMURA, J. G. HAMILTON, J. J. ROONEY, *Organometallics*, **1998**, 17, 4183–4195, (d) V. AMIR-EBRAHIMI, D. A. K. CORRY, J. G. HAMILTON, J. M. THOMPSON, J. J. ROONEY, *Macromolecules*, **2000**, 33, 717–724. (e) W. J. FEAST, V. C. GIBSON, K. J. IVIN, E. KHOSRAVI, A. M. KENWRIGHT, E. L. MARSHALL, J. P. MITCHELL, *Macromol. Chem.*, **1992**, 193, 2103–2111, (f) J. G. HAMILTON, U. FRENZEL, F. J. KOHL, T. WESKAMP, J. J. ROONEY, W. A. HERRMANN, O. NUYKEN, *J. Organomet. Chem.*, **2000**, 606, 8–12.
- 36 K. J. IVIN, G. LAPIENIS, J. J. ROONEY, *Polymer*, **1980**, 21, 436–443.
- 37 H. T. HO, K. J. IVIN, J. J. ROONEY, *J. Mol. Catal.*, **1982**, 15, 245–270.
- 38 T. SUNAGA, K. J. IVIN, G. E. HOFMEISTER, J. H. OSKAM, R. R. SCHROCK, *Macromolecules*, **1994**, 27, 4043–4050.

- 39 R. SAF, K. FABER, G. PEN, H. GRIENGL, *Tetrahedron*, **1988**, *44*, 389–392.
- 40 D. D. MANNING, X. HU, P. BECK, L. L. KIESSLING, *J. Am. Chem. Soc.*, **1997**, *119*, 3161–3162.
- 41 R. M. E. SCHITTER, T. STEINHAUSLER, F. STELZER, *J. Mol. Catal. A: Chemical*, **1997**, *115*, 11–20.
- 42 G. R. DAVIES, H. V. ST A. HUBBARD, I. M. WARD, W. J. FEAST, V. C. GIBSON, E. KHOSRAVI, E. L. MARSHALL, *Polymer*, **1995**, *36*, 235–243.
- 43 J. G. HAMILTON, K. J. IVIN, J. J. ROONEY, *J. Mol. Catal.*, **1986**, *36*, 115–125.
- 44 J. M. DESIMONE, C. MISTELE, J. G. HAMILTON, J. J. ROONEY, *Macromolecules*, **1998**, *31*, 4387–4389.
- 45 V. AMIR-EBRAHIMI, A. G. CARVILL, J. G. HAMILTON, J. J. ROONEY, C. TUFFY, *J. Mol. Catal. A: Chemical*, **1997**, *115*, 85–94.
- 46 R. R. SCHROCK, J. FELDMAN, L. F. CANNIZZO, R. H. GRUBBS, *Macromolecules*, **1987**, *20*, 1172–1174.
- 47 W. J. FEAST, V. C. GIBSON, E. KHOSRAVI, E. L. MARSHALL, *J. Chem. Soc., Chem. Commun.*, **1994**, 9–10.
- 48 M. NORTH in reference [1e], page 157.
- 49 K. J. IVIN, A. M. KENWRIGHT, E. KHOSRAVI, J. G. HAMILTON, *Macromol. Chem. Phys.*, **2001**, *202*, 3624–3633.
- 50 G. WIDAWSKI, W. J. FEAST, P. DOUNIS, *J. Mater. Chem.*, **1995**, *5*, 1847–1851.
- 51 R. G. DAVIES, V. C. GIBSON, M. NORTH, D. A. ROBSON, *Polymer*, **1999**, *40*, 5239–5241.
- 52 J. G. HAMILTON, K. J. IVIN, unpublished results.
- 53 M. G. PERROTT, B. M. NOVAK, *Macromolecules*, **1996**, *29*, 1817–1823.
- 54 L. PU, W. WAGAMAN, R. H. GRUBBS, *Macromolecules*, **1996**, *29*, 1138–1143.
- 55 L. R. SITA, S. R. LYON, *J. Am. Chem. Soc.*, **1993**, *115*, 10374–10375.
- 56 R. H. GRUBBS, Z. WU, *J. Mol. Catal.*, **1994**, *90*, 39–42.
- 57 J. G. HAMILTON, K. J. IVIN, G. M. MCCANN, J. J. ROONEY, *J. Chem. Soc., Chem. Commun.*, **1984**, 1379–1381.
- 58 W. J. FEAST, V. C. GIBSON, E. L. MARSHALL, *J. Chem. Soc., Chem. Commun.*, **1992**, 1157–1158.
- 59 J. BROEDERS, W. J. FEAST, V. C. GIBSON, E. KHOSRAVI, *J. Chem. Soc., Chem. Commun.*, **1995**, 343–344.
- 60 R. R. SCHROCK, J.-K. LEE, R. O'DELL, J. H. OSKAM, *Macromolecules*, **1995**, *28*, 5933–5940.
- 61 V. PERCEC, D. SCHLUETER, *Macromolecules*, **1997**, *30*, 5783–5790.
- 62 S. MEIER, H. REISINGER, R. HAAG, S. MECKING, R. MULHAUPT, F. STELZER, *J. Chem. Soc., Chem. Commun.*, **2001**, 855–856.
- 63 C. P. BALL, A. G. M. BARRETT, L. F. POITOUT, M. L. SMITH, Z. E. THORN, *J. Chem. Soc., Chem. Commun.*, **1998**, 2453–2454.
- 64 Z. WU, A. D. BENEDICTO, R. H. GRUBBS, *Macromolecules*, **1993**, *26*, 4975–4977.
- 65 J. G. HAMILTON, J. J. ROONEY, unpublished results.
- 66 R. CHARVET, B. M. NOVAK, *Macromolecules*, **2001**, *34*, 7680–7685.
- 67 C. W. BIELAWSKI, R. H. GRUBBS, *Angew. Chem. Int. Ed.*, **2000**, *39*, 2903–2906.
- 68 H. E. ARDILL, R. M. E. GREENE, J. G. HAMILTON, H. T. HO, K. J. IVIN, G. LAPIENIS, G. M. MCCANN, J. J. ROONEY, in ACS Symposium Series 286, Ed. J. E. McGRATH, American Chemical Society, Washington, 1985.
- 69 L. DELAUDE, A. DEMONCEAU, A. F. NOELS, *Macromolecules*, **1999**, *32*, 2091–2103.
- 70 J. G. HAMILTON, K. J. IVIN, G. M. MCCANN, J. J. ROONEY, *Macromol. Chem.*, **1985**, *186*, 1477–1494.
- 71 Z. WU, S. T. NGUYEN, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.*, **1995**, *117*, 5503–5511.
- 72 K. J. IVIN, D. T. LAVERTY, J. J. ROONEY, *Makromol. Chem.*, **1978**, *179*, 253–258.
- 73 K. J. IVIN, D. T. LAVERTY, J. H. O'DONNELL, J. J. ROONEY, C. D. STEWART, *Makromol. Chem.*, **1979**, *180*, 1989–2000.
- 74 R. M. E. GREENE, J. G. HAMILTON, K. J. IVIN, J. J. ROONEY, *Makromol. Chem.*, **1986**, *187*, 619–632.
- 75 H. H. BRINTZINGER, D. FISCHER, R. MULHAUPT, B. RIEGER, R. M. WAYMOUTH, *Angew. Chem. Int. Ed.*, **1995**, *34*, 1143–1170.

- 76 P. SCHWAB, M. B. FRANCE, J. W. ZILLER, R. H. GRUBBS, *Angew. Chem. In. Ed.*, **1995**, 34, 2039–2041.
- 77 W. J. FEAST, V. C. GIBSON, K. J. IVIN, A. M. KENWRIGHT, E. KHOSRAVI, *J. Chem. Soc., Chem. Commun.*, **1994**, 1399–1400.
- 78 J. G. HAMILTON, K. J. IVIN, J. J. ROONEY, L. C. WARING, *J. Chem. Soc., Chem. Commun.*, **1983**, 159–161.
- 79 K. M. TOTLAND, T. J. BOYD, G. G. LAVOIE, W. M. DAVIS, R. R. SCHROCK, *Macromolecules*, **1996**, 29, 6114–6125.
- 80 A. ABELE, R. WURSCHE, M. KLINGA, B. RIEGER, *J. Mol. Catal. A: Chemical*, **2000**, 160, 20–30.
- 81 Y.-X. CHEN, C. L. STERN, T. J. MARKS, *J. Am. Chem. Soc.*, **1997**, 119, 2582–2583.
- 82 (a) T. J. SEIDERS, D. W. WARD, R. H. GRUBBS, *Org. Lett.*, **2001**, 3, 3225–3228, (b) H. WAKAMATSU, S. BLECHERT, *Angew. Chem. In. Ed.*, **2002**, 41, 764–796, (c) J. J. VAN ELDHUIZEN, S. B. GARBER, J. S. KINGSBURY, A. H. HOVEYDA, *J. Am. Chem. Soc.*, **2002**, 124, 4954–4955.
- 83 J. E. HAMLIN, K. HIRAI, A. MILLAN, P. M. MAITLIS, *J. Mol. Catal.*, **1980**, 7, 543–last page.
- 84 J. BOOR, *Ziegler-Natta Catalysts and Polymerizations*, Academic Press, New York, 1979.

3.6

Syntheses and Applications of Bioactive Polymers Generated by Ring-Opening Metathesis Polymerization

Laura L. Kiessling and Robert M. Owen

3.6.1

Introduction

Complex macromolecular interactions govern most biological processes, and misregulation of these interactions can lead to disease. Consequently, there is intense interest in elucidating the molecular basis for these interactions and in developing tools to manipulate them. In many instances, these complex processes are governed by multivalent interactions, i.e., complexes in which multiple ligands interact with their target receptors [1–3]. Multivalent binding can play an important role in regulating the specificity and avidity of biological processes. Because of the diversity and complexity of naturally occurring multivalent ligands, the design and synthesis of novel scaffolds for the presentation of biologically active epitopes is an area of research that has attracted considerable attention [4–10]. One of the major advantages of synthetic multivalent displays is that they can be customized. In principle, many synthetic scaffolds allow for the systematic variation of different parameters such as ligand valency or orientation. This variation can be used both to optimize a display for a particular activity (e.g., tighter binding avidity) and to probe the mechanistic underpinnings of a biological system. Another advantage of synthetic displays is their generality. Although synthetic multivalent ligands are often designed to mimic naturally occurring scaffolds such as glycoproteins, polypeptides, or DNA, non-natural, synthetic scaffolds can also be used to construct novel displays of biologically active epitopes that do not have naturally occurring counterparts. Such ligands can be used to probe systems that would be inaccessible using naturally occurring ligands. Consequently, synthetic scaffolds represent a set of valuable tools for exploring a wide range of complex macromolecular interactions.

One attractive approach to the synthesis of non-natural displays is the use of a polymeric scaffold that can be constructed quickly from relatively simple starting materials [9]. However, there are several considerations that must be taken into account when utilizing this approach. The first major issue is the method in which the bioactive epitopes are introduced (Figure 3.6-1). Polymerization of a monomer containing the ligand of interest is conceptually the most straightforward method.

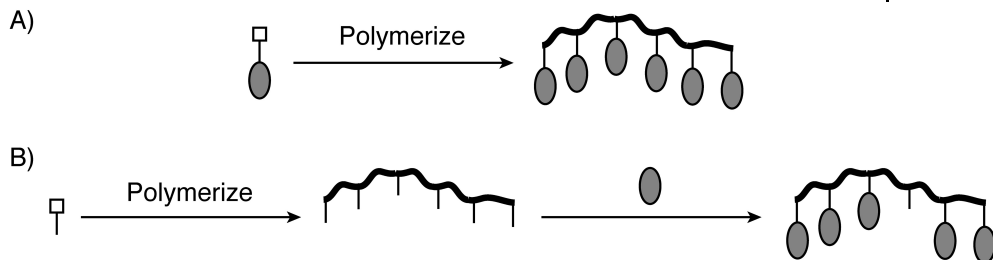


Fig. 3.6-1. Two general methods for the synthesis of polymers containing bioactive epitopes. (A) The desired epitopes can be introduced prior to the polymerization or (B) subsequent to the polymerization reaction.

Its application yields polymers with the highest density of functional groups displayed along the polymer backbone. This approach can be difficult to implement if there are incompatibilities between the solubility of the initiator, the monomer or the growing polymer chain in the polymerization solvent. Another potential limitation is the compatibility of the polymerization reaction with the polar functional groups typically found in biologically active epitopes. Although these limitations can be overcome with appropriate protecting groups, deprotection conditions for the fully formed polymer can be difficult to optimize (*vide infra*). Moreover, polymers with a lower level of ligand loading are often desired. While these can be generated using two different monomers, different rates of incorporation can lead to a non-random distribution of binding epitopes. The second approach, typically described as post-polymerization modification (PPM), relies on introduction of the epitope of interest subsequent to monomer polymerization. The PPM method is a more general approach to the synthesis of multivalent ligands and can overcome the problems described above. However, the conjugation chemistry employed must be efficient as well as chemoselective. The choice between these two strategies can be driven by both the nature of the ligand and the type of polymerization reaction employed. The examples outlined in this chapter demonstrate the successful use of both of these strategies in the synthesis of bioactive displays using ring-opening metathesis polymerization (ROMP).

The second consideration in using a polymer-based scaffold for biological studies is the heterogeneity (or polydispersity) of the polymeric ligand. For example, polymers generated under free-radical conditions have been utilized extensively as scaffolds for displaying biologically active binding epitopes [7, 11–18]. The polymerization reaction is tolerant of a variety of functional groups and it can be conducted under aqueous conditions. Consequently, it is well suited to the polymerization of monomers containing fully deprotected ligands. Despite these advantages, materials generated using standard free-radical polymerization reactions are polydisperse and are not amenable to systematic, mechanistic studies. For many applications (*vide infra*), it is advantageous to employ a polymerization strategy that affords more homogeneous materials. To address these requirements, researches have explored a range of controlled polymerization strategies for the

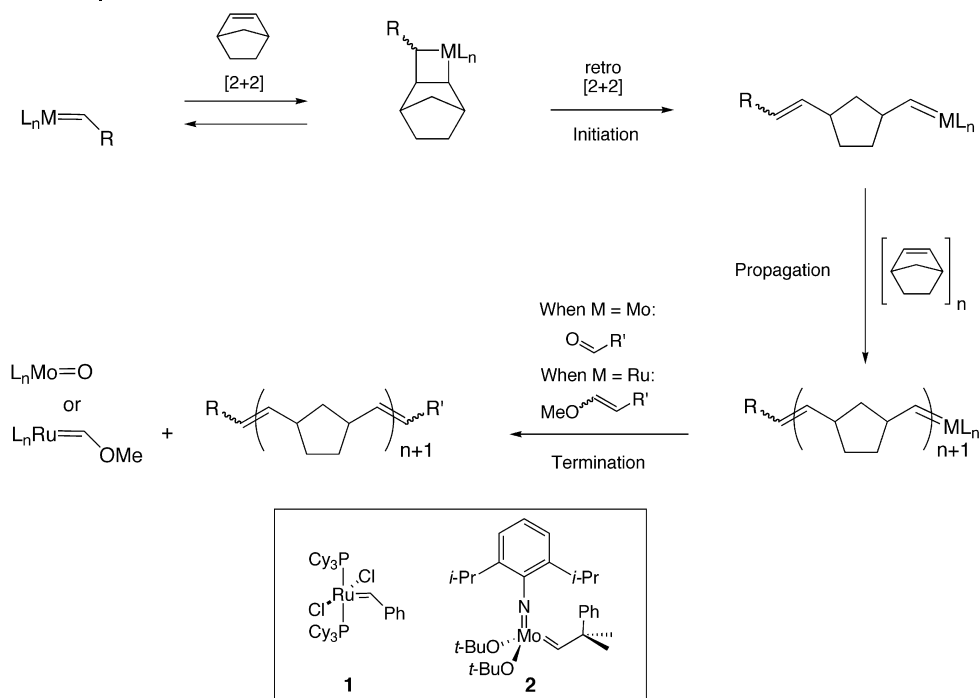


Fig. 3.6-2. Chauvin mechanism for the ring-opening metathesis polymerization (ROMP) catalyzed by metal-carbene initiators. Examples of ruthenium (1) and molybdenum carbenes (2) that promote ROMP are shown.

synthesis of polymers containing biologically active epitopes [19–30]. One of the most versatile is ROMP.

ROMP has received considerable attention due to its living nature and functional group tolerance (*vide infra*). The Chauvin mechanism [31] for ROMP is outlined in Figure 3.6-2. Association of the metal carbene with the double bond of the monomer unit followed by a [2+2] cycloaddition generates a metallacyclobutane intermediate. Retro [2+2] cycloaddition leads to a new metal carbene that reacts with subsequent monomer units in the same manner to propagate the polymer chain. Upon complete consumption of the monomer in solution, the polymerization can be terminated in a controlled fashion. Polymerization reactions mediated by either of the defined initiators 1 or 2 [32, 33] are generally classified as living polymerizations, in which chain termination and transfer events are much slower than chain propagation [30]. These characteristics allow for the synthesis of polymers and block copolymers with defined lengths and low polydispersities when initiation rates exceed those of propagation. Furthermore, the controlled termination of the polymerization reactions with either aldehydes for the molybdenum carbene-initiated or electron-rich olefins for the ruthenium carbene-initiated processes pro-

vides an opportunity for the synthesis of materials containing a defined end label [34–38]. Thus, ROMP provides a means to rapidly synthesize defined polymers with unique structural features that contain biologically relevant epitopes.

The ruthenium- and molybdenum-carbene catalysts possess differences in their chemical reactivity that are important for their use as reagents for generating bioactive polymers. The molybdenum initiators are highly reactive and typically provide polymers with low polydispersity index (PDI) values. These initiators can also be used to control the stereochemistry and tacticity of the polymer backbone [33]. However, they exhibit limited tolerance toward oxygen-containing functional groups and are very sensitive to trace amounts of oxygen and water in the reaction system. Ruthenium-carbene initiators are tolerant of a much wider range of biologically relevant functional groups and are much less sensitive to trace impurities than are their molybdenum counterparts [39]. Although the ruthenium initiators generally produce polymers with slightly broader molecular weight distributions, the reactivity of the ruthenium-carbene initiators can be tuned by modifying the nature of the phosphine ligand to yield polymers with improved PDI values [40, 41]. As a result, these ruthenium-carbene initiators are used widely in the synthesis of polymers that contain biologically active epitopes. Moreover, recent developments in catalyst design have produced ruthenium initiators that give rise to polymers that possess very narrow PDI values [42].

Many different research groups have applied ROMP to the synthesis of a diverse range of multivalent ligands that contain biologically relevant epitopes. In the first section of this chapter, we will present examples and discuss the synthetic hurdles that arise in the polymerization of norbornene-based monomers that contain biologically relevant, polar functional groups. We also will review recent developments in bioactive polymer synthesis that further extend the utility of materials generated by ROMP, including strategies for the post-polymerization modification (PPM) of ROMP-generated polymers with biological epitopes and selective end-capping strategies. Finally, this review also provides an overview of the biological applications of ROMP-generated materials. The power of the resulting materials in biochemical and biophysical investigations is highlighted.

3.6.2

Synthesis of Biologically Active Polymeric Displays

3.6.2.1

Carbohydrate-Containing Polymeric Displays

Synthesis of carbohydrate-substituted polymers with RuCl_3 The synthesis of linear polymers that present multiple sugar epitopes constitutes one of the most widely explored biological applications of ROMP. Initial investigation of the feasibility of ROMP for the preparation of sugar-substituted polymers utilized the polymerization of sugar-substituted norbornene monomers with RuCl_3 . Grubbs and coworkers had previously demonstrated that ROMP initiated with the hydroxyl

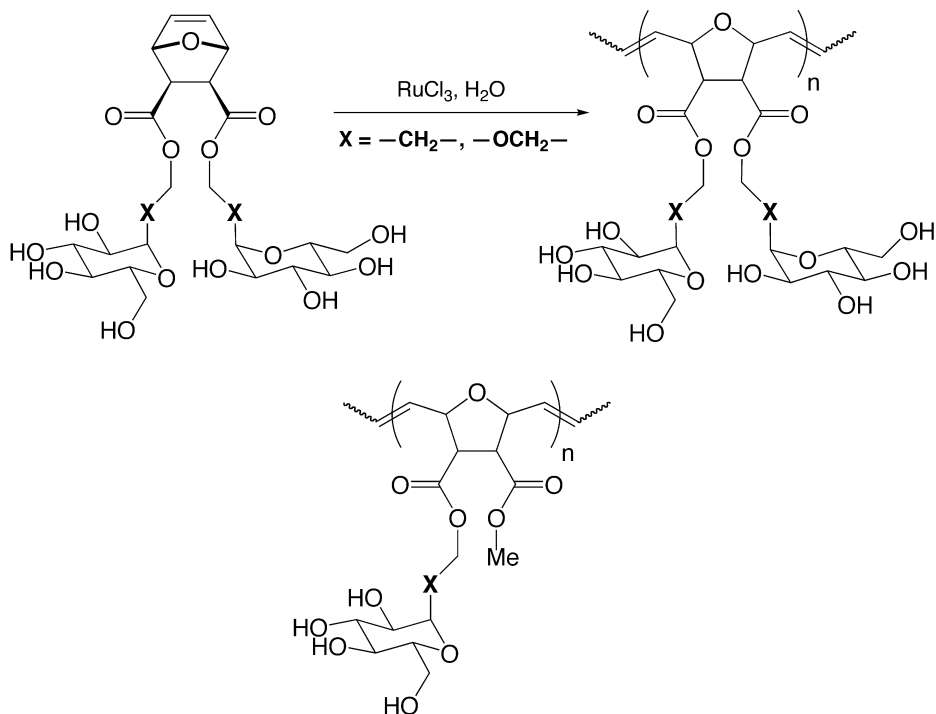


Fig. 3.6-3. Demonstration of the utility of ROMP for synthesizing carbohydrate-substituted polymers. This technology was successfully applied to the synthesis of

displays of different density (higher or lower degree of substitution) glucose or mannose epitopes.

group-tolerant RuCl_3 provided polymers with good PDI values (1.2) [43]. Using this process, Kiessling and coworkers constructed a series of monomers consisting of 7-oxanorbornene derivatized with two glucose or mannose epitopes by either a C- or an O-glycosidic linkage (Figure 3.6-3) [44]. Each monomer was efficiently polymerized by RuCl_3 in water at 55 °C to yield the sugar-substituted polymers in yields ranging from 60% to 80%. Molecular mass analysis of the polymers by gel filtration chromatography indicated a molecular mass of 10^6 relative to dextran standards. To remove ruthenium contaminants from the polymers, the authors also explored an alternate strategy in which the active propagating species was preformed before addition to the bulk monomer. This second method provided the desired polymers in improved yields and had lengths comparable to polymers synthesized by the first method. In a subsequent publication, this second polymerization technique was also successfully applied to the synthesis of polymers that display a lower density of saccharide epitope per monomer unit (Figure 3.6-3) [45]. Polymerization of monosubstituted 7-oxanorbornene-based monomers with preformed initiator yielded polymers with relative molecular weights of 10^6 in approximately 60% yield. Thus, these results indicate that carbohydrate-substituted

ligands can be synthesized via ROMP, although control over the synthesis of the resulting materials was limited using this undefined catalyst.

Synthesis of carbohydrate-substituted polymers with defined initiators Grubbs and Fraser explored the synthesis of carbohydrate-substituted polymers using the defined ruthenium carbene catalyst **3** (Figure 3.6-4A) [46, 47]. They initially investigated the polymerization of monomers containing various protected glucose derivatives. Interestingly, the rate of the polymerization and the characteristics of the resulting polymers were highly dependent upon the protecting group on the sugar. The acetate-protected sugars were the most reactive and produced polymers in good yields (70%) but with very high PDI values (2.1). The benzyl-protected monomers reacted more slowly than the acetate-protected monomers but provided

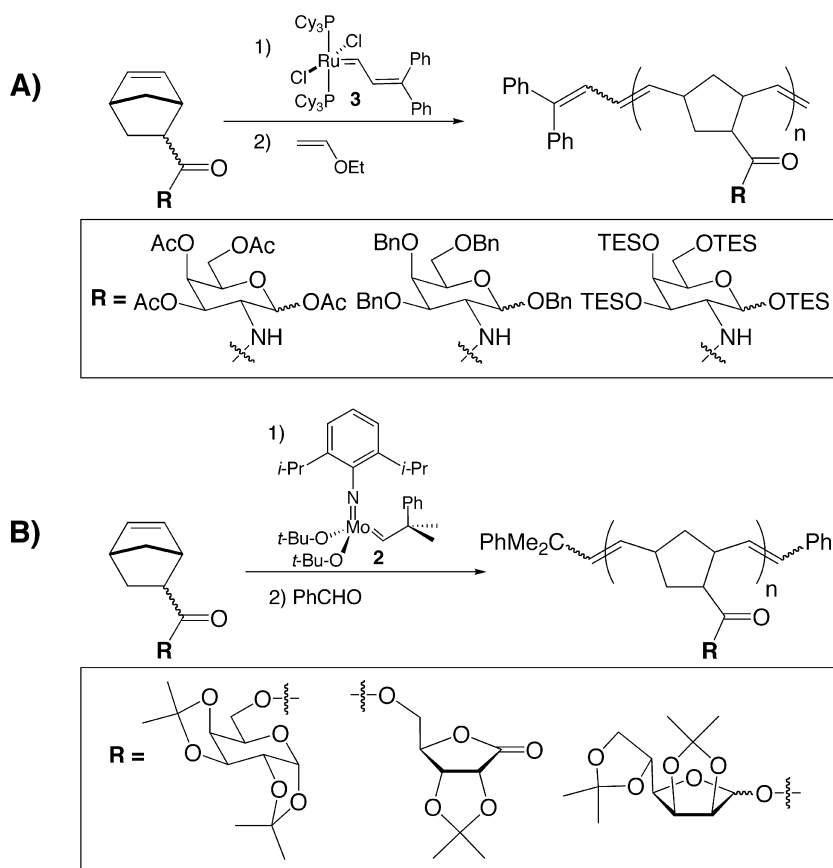


Fig. 3.6-4. Synthesis of carbohydrate-substituted polymers with defined initiators. (A) Polymers synthesized by Grubbs and Fraser using ruthenium initiator **3**. (B) Schrock and coworkers' approach to carbohydrate-substituted polymers synthesized with a molybdenum alkylidene **2**.

polymers in improved yields (91%) and PDI values (1.2). The silyl-protected monomers reacted the slowest of all three monomers and provided the polymers with the best PDI values (1.1–1.2), although the yields were generally not as high (45–78%). In addition, simple random and diblock copolymers containing norbornene and the acetate-protected carbohydrate-substituted monomer could be constructed. When the benzyl- and acetate-protected polymers were subjected to conditions for protecting-group removal, complex mixtures of partially deprotected products were obtained. In contrast, deprotection of the silyl-protected polymers occurred efficiently with tetrabutylammonium fluoride (TBAF) to yield the desired polymers. These studies demonstrated that defined ruthenium carbenes could be used to produce carbohydrate-substituted polymers. Thus, they suggested that ROMP might be used to afford tailored, biologically active materials.

Schrock's molybdenum-carbene initiator was also utilized in the synthesis of sugar-substituted polymers [48]. Schrock and coworkers polymerized four monomers bearing protected galactose, ribose, and mannose moieties (Figure 3.6-4B). The cyclic acetal protecting group was used to mask hydroxyl groups because of the range of conditions that can be used to remove it. Yields for each of the polymers were generally >96%, with PDI values that ranged from 1.02–1.25. Light-scattering analysis demonstrated a linear relationship between the monomer:initiator ratio (M:I) and the observed average molecular weight, which suggests that the polymerization reactions were living. Copolymers containing two, three, or four different monomer units could also be generated by this method. Yields (>90%) and PDI values (<1.2) were excellent for these polymers and were independent of the order of addition of the monomers. Unfortunately, successful removal of the cyclic acetals with trifluoroacetic acid was substrate specific. Polymers displaying galactose residues could be generated successfully; however, the authors were unable to isolate intact polymeric displays of the ribose or mannose residues. Like the studies of Fraser and Grubbs, these investigations provided impetus to explore ROMP as a method to generate biologically active materials.

Polymerization of unprotected sugar epitopes with defined initiators Despite their potential utility, the examples containing protected monomers underscore the potential problems associated with protecting-group removal subsequent to the polymerization reaction. Conditions successfully optimized for the monomer are often ineffective for the polymeric display. Moreover, characterization of the resulting mixture of products is often challenging. Elimination of a final protecting-group removal step would allow for the synthesis of materials containing sensitive carbohydrate epitopes such as sulfated sugars, biologically relevant polysaccharides, or other sensitive functionality. Consequently, the ability to synthesize substituted polymers utilizing both defined initiators and unprotected monomer units constituted a critical advance in the synthesis of sugar-substituted, polymeric displays via ROMP. Such a methodology increases diversity of binding epitopes that could be incorporated and, hence, the scope of the biological questions addressed.

Grubbs and coworkers provided the first example of ROMP of monomers containing unprotected sugars using a defined initiator (Figure 3.6-5A) [46]. To overcome solubility differences between the catalyst and the growing polymer chain, they utilized a mixed solvent system of water and CH_2Cl_2 that contained a cationic emulsifier, dodecyltrimethylammonium bromide (DTAB). Using these conditions, a glucose-substituted polymer was produced in 99% yield. The PDI of the polymer was not determined; however, polymers generated under similar conditions have been reported with PDI values ≤ 1.1 [49]. These data suggest that polymerization reactions conducted under these conditions may be living and therefore applicable to the synthesis of defined biological probes. Emulsion conditions have been used subsequently in the synthesis of polymeric displays that contain disaccharides [50], sulfated monosaccharides [51–53], and complex sulfated and non-sulfated trisaccharides (Figure 3.6-5B) [54, 55].

Kiessling and coworkers reported a complementary set of conditions for the polymerization of monomers bearing unprotected monosaccharides (Figure 3.6-5C) [56]. Initiation was performed in a mixture of methanol, water, and CH_2Cl_2 ; water and methanol were subsequently added to dissolve the resulting oil. These conditions produced polymers that had a degree of polymerization (DP, determined from the NMR spectrum) that ranged from 10 to 52, depending upon the initial M:I ratio employed. These conditions were found to provide a higher degree of linearity between M:I and the polymer length than do standard emulsion conditions. The linear relationship between M:I and DP suggests that these conditions provide a living polymerization when $\text{M:I} \leq 50$. Gel permeation chromatography (GPC) characterization of the acetylated polymer with $\text{DP} = 10$ suggested that these conditions yield polymers with PDI values of ≤ 1.2 [57]. Although polymers with DP greater than 50 could not be generated using these conditions, this methodology provides an alternative to the previously reported emulsion conditions for the synthesis of shorter oligomers of unprotected carbohydrate-substituted polymers with well-defined lengths.

Synthesis of linear carbohydrate analogue polymers Glycoproteins and glycolipids are two major classes of glycoconjugates. In each of these materials, multiple copies of saccharides are displayed from a core structure. Most of the examples of ROMP-generated, carbohydrate-substituted polymers have focused upon mimics of glycoproteins or glycolipid arrays. There is, however, another class of important glycomaterials, namely, polysaccharides composed entirely of monosaccharides linked by glycosidic bonds. Mülhaupt and coworkers recently described the synthesis of polyribose mimics via ROMP (Figure 3.6-6) [58]. Polymerization of cyclic acetal-protected 2-*endo* and 3-*exo*-7-oxanorbornene diol with Grubbs' catalyst (1) gave polymers with PDI values of 1.4–1.5. To more effectively mimic the hydroxylation pattern of ribose, the polymer backbone was dihydroxylated using catalytic OsO_4 and the acetal groups were removed by hydrolysis. The resulting materials provide an interesting example of a new application of ROMP for the synthesis of carbohydrate-based materials.

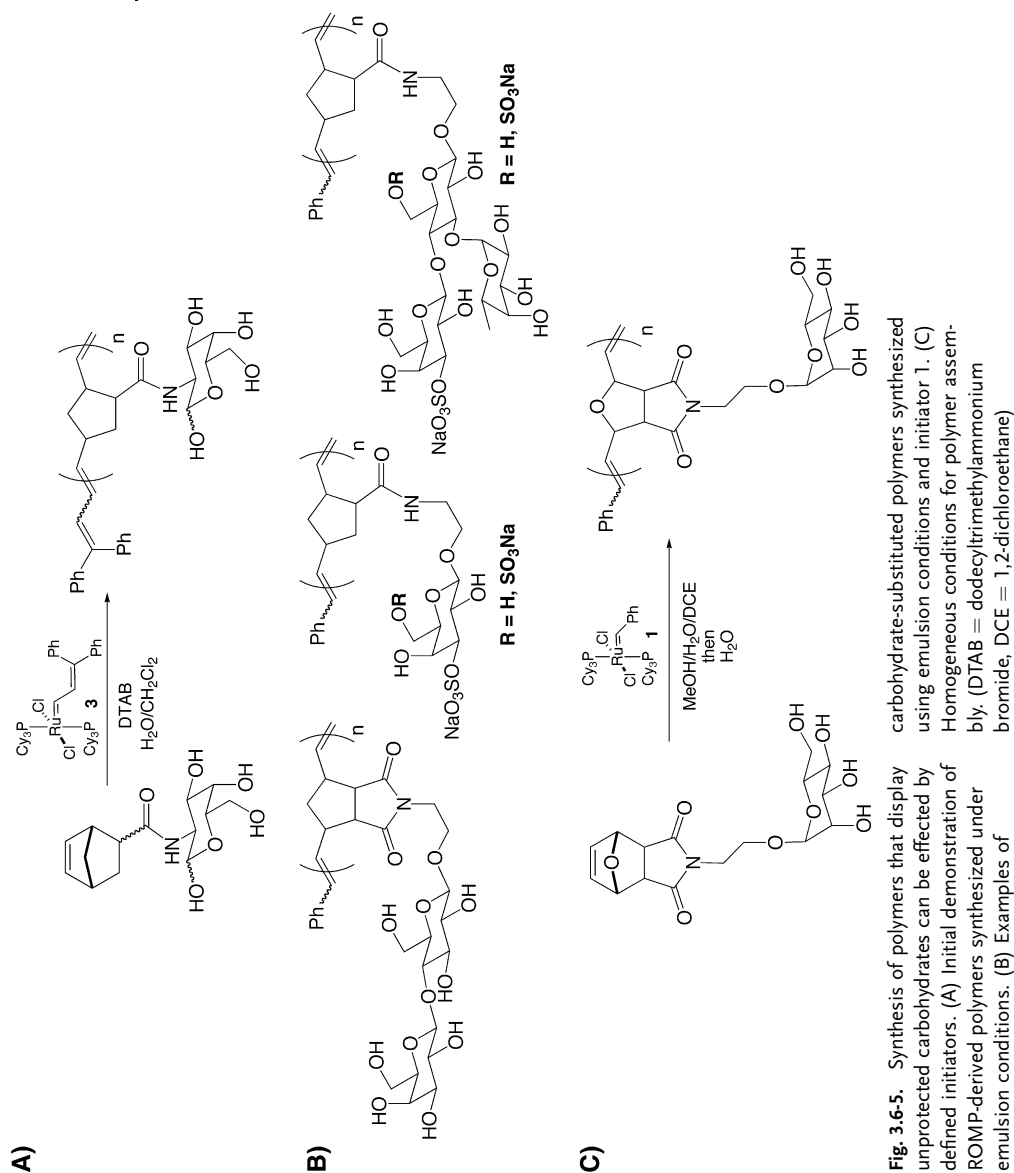


Fig. 3.6-5. Synthesis of polymers that display unprotected carbohydrates can be effected by defined initiators. (A) Initial demonstration of ROMP-derived polymers synthesized under emulsion conditions. (B) Examples of

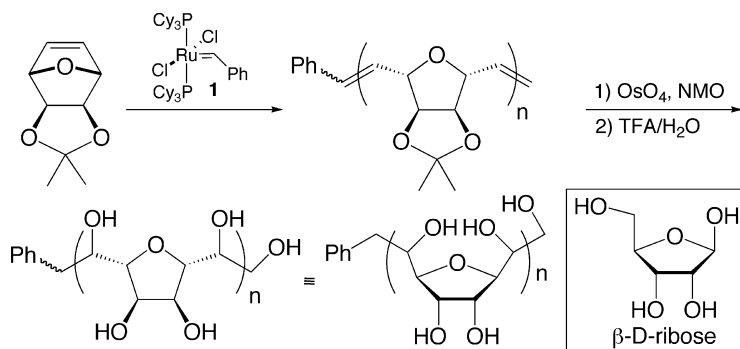


Fig. 3.6-6. Application of ROMP to the synthesis of mimics of linear carbohydrate polymers. Ribose is shown for comparison. (TFA = trifluoroacetic acid, NMO = N-methylmorpholine-N-oxide)

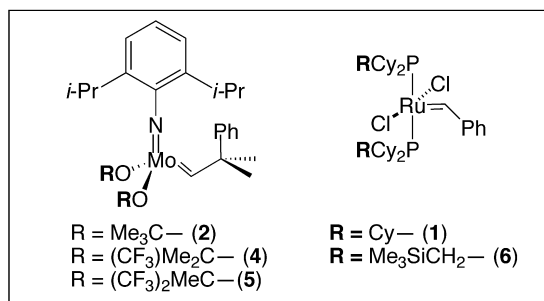
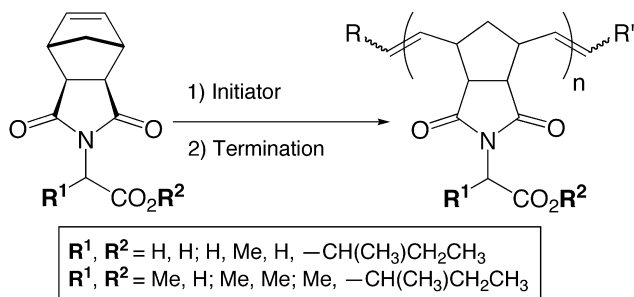
3.6.2.2

Peptide-Substituted Polymers

Concurrent with the initial reports describing the synthesis of carbohydrate-functionalized polymers, Gibson and coworkers explored the feasibility of using ROMP to generate polymers containing modified amino acids. In their initial studies, they utilized Schrock's molybdenum-carbene initiators for the polymerizations of amino-ester functionalized monomers (Figure 3.6-7A) [59, 60]. Each of the monomers polymerized efficiently in benzene, with M:I ratios ranging from 30:1 to 100:1. PDI values for the polymers were generally good, with most between 1.1 and 1.3. However, reaction times had to be carefully controlled with the more electrophilic initiators (4 and 5). Secondary metathesis reactions occur with these initiators, leading to polymers with broadened molecular weight distributions. The backbone double bond stereochemistry could be controlled by the type of initiator employed; the more electrophilic molybdenum-carbene catalysts provided polymers with higher *cis* alkene content. These differences in *cis:trans* content provided polymers with different physical properties as measured by their glass transition temperatures. Thus, these examples successfully demonstrate the applicability of ROMP for the synthesis of polymers displaying simple amino acid side chains.

On the basis of these initial studies, Gibson and coworkers also sought to prepare polymers that possess amino acid derivatives with free carboxylic acid groups (Figure 3.6-7A) [61]. The incompatibility of the molybdenum initiators with carboxylic acid groups prompted them to investigate Grubbs' catalyst (1) for the polymerization reactions. The amino acid- and amino ester-derived monomers were polymerized in THF or CH₂Cl₂, respectively, with M:I ratios of 50:1 to 100:1. The PDI values for these polymers were acceptable (1.2–1.4), although they were not as low as those obtained with the molybdenum initiators. One possible explanation for the broader PDI values is that a significant amount of uninitiated catalyst was

A)



B)

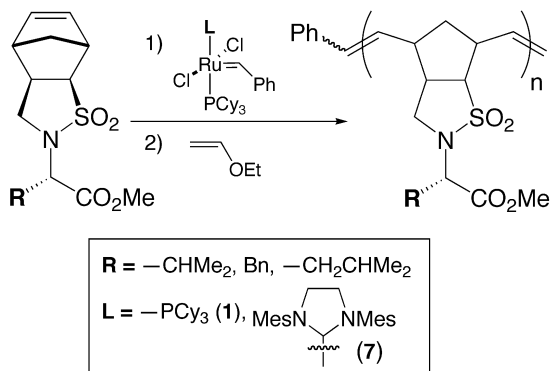


Fig. 3.6-7. Synthesis of polymers that display amino acid side chains. (A) Gibson and coworkers' studies of simple amino acid- and ester-substituted polymers using both molyb-

denum- and ruthenium-carbene initiators. (B) Nguyen and coworkers' synthesis of polymers containing sulfonamide-derived amino esters. (MES = mesityl)

observed at the end of the polymerization, even when M:I ratios of 50:1 were employed. To circumvent this problem, Gibson and coworkers developed a modified version of the Grubbs' catalyst (**6**) [41] that afforded that polymers with improved PDI values (1.05–1.1); no uninitiated catalyst was detected for any of the monomers investigated.

Hanson and coworkers have also explored the polymerization of amino acid-based monomers with the stated purpose of developing new biopolymers containing sulfonamide groups (Figure 3.6-7B) [62]. Polymerization reactions initiated with Grubbs' first- (1) and second-generation (7) [63] catalysts proceeded efficiently to give polymers with PDI values of 1.1–1.2. Gibson and Hanson's synthetic methods have the potential to produce a new class of novel, defined biomaterials. The ability of these materials to function in this capacity however, has not yet been addressed.

ROMP-derived polymers also have been utilized as defined scaffolds for presenting bioactive peptides. Grubbs and coworkers described the synthesis of polymers that contain Arg-Gly-Asp (RGD) and Ser-Arg-Asn (SRN) sequences (Figure 3.6-8) as potential chemotherapeutics [64]. Different monomers were tested by polymerizing a range of norbornene or oxanorbornene derivatives that contained a single protected amino acid. On the basis of the synthetic accessibility of the monomers and the PDI values of the resulting polymers, monomers derived from 5-norbornene-*exo*-2-carboxylic acid were employed. These monomers could be polymerized in near quantitative yield to afford material with a PDI of 1.15. The monomer was then derivatized with the desired GRGD- or SRN-protected peptide sequences or a pentaethylene glycol moiety. Initial attempts to polymerize mixtures of these monomers with Grubbs' ruthenium initiator (1) were successful only when the polymerization contained 10% of the RGD-substituted monomer and 90% of ethylene glycol-substituted monomer. When the mole fraction of the peptide-containing monomers in the reaction mixture was increased, low yields of the resulting polymers were obtained. Furthermore, many of the resulting polymers had bimodal molecular weight distributions. By using the more active dihydroimidazolyldiene-substituted catalysts (7), a series of random copolymers could be synthesized in modest to excellent yields (32–92%) with moderate PDI values (1.2–1.7). The relative amount of each epitope in the polymers corresponded to the mole fraction of the different monomers employed, suggesting that each monomer was polymerized with equal efficiency. Interestingly, although initiator 1 gave a highly *trans*-biased backbone, polymerization with the more active catalyst 6 produced polymers with a higher *cis* content. The side chain-protecting groups of most of the polymers could be efficiently removed with trifluoroacetic acid. However, removal of the protecting groups on the SRN-substituted polymers required treatment with HF due to limited solubility of the partially deprotected polymer in trifluoroacetic acid. Subsequent to this initial publication, Grubbs and coworkers reported a second set of monomers and polymers with slightly more complex peptide sequences [65]. Using the same conditions as before, they synthesized homopolymers of Gly-Arg-Gly-Asp-Ser (GRGDS), Gly-Arg-Gly-Glu-Ser (GRGES), and a random copolymer containing a 1:1 ratio of GRGDS and Pro-His-Ser-Arg-Asn (PHSRN) epitopes. Yields (64–91%) and PDI values (1.3–1.4) were comparable to those obtained in their initial studies. Protecting-group removal effected by trifluoroacetic acid or HF yielded the desired water-soluble polymers. These studies indicate that polymers that present polar amino acids and short oligopeptides can be accessed via ROMP.

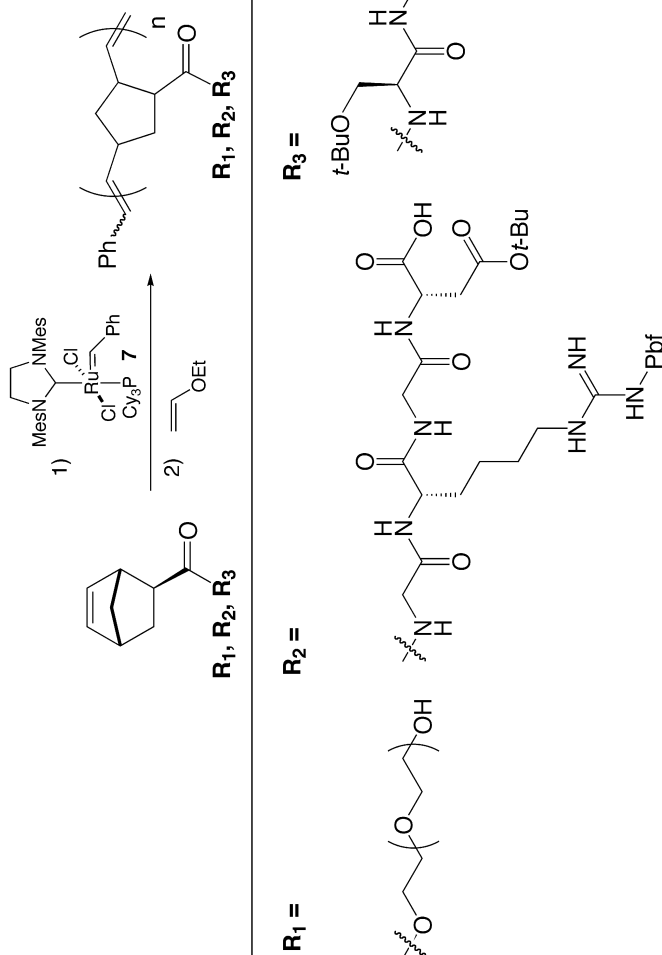


Fig. 3.6-8. Synthesis of polymers that contain three epitopes using the more active, second-generation Grubbs' catalyst (7). (Pbf = 2,2,4,6,7-pentamethylidihydrobenzofuran-5-sulfonyl, Trt = trityl)

3.6.2.3

Synthesis of DNA/Polymer Conjugates via ROMP

The development of synthetic mimics of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) is an area of research that has attracted considerable attention over the last decade. One area of focus is the development of molecules that retain the recognition specificity of DNA or RNA but possess different properties such as increased stability or enhanced hybridization potency [66, 67]. To attain these goals, researchers have developed a range of non-natural backbones from which standard base pairs are displayed, including phosphorothioates, peptides, and vinyl polymers. In a similar manner, Gibson and coworkers have explored the utility of a ROMP-generated backbone for constructing DNA mimics. After their initial report of thymine-functionalized polymers [68], Gibson and coworkers reported on studies directed towards the synthesis of homopolymers that contain each of the natural nucleic acid bases using ROMP (Figure 3.6-9) [69]. Each of the bases (thymine, adenine, cytosine, guanine, and uracil) was linked to an imide-based monomer via either an amide or ester group. To minimize steps involving protecting-group removal, the researchers employed monomers bearing unprotected nucleoside bases in the polymerization reactions. Unfortunately, most of these monomers had limited solubility in appropriate polymerization solvents. Although the solubility of some of the monomers could be improved with the

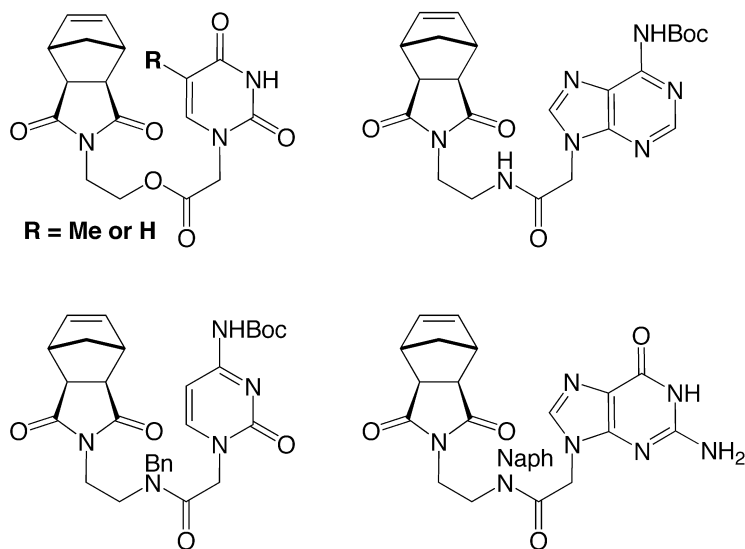


Fig. 3.6-9. Representative monomers investigated by Gibson and coworkers in their synthesis of polymers containing nucleic-acid bases. The bases substituted include thymine (or uracil), protected adenine, protected cytidine, and guanine derivatives (left to right).

The syntheses of the corresponding polymers proved challenging due to differences in solubility between the reactants and the products. (Boc = tert-butyl carbamate, Bn = benzyl, Naph = naphthyl)

addition of hydrophobic moieties, polymerization of these monomers with either initiator **1** or **6** met with limited success. Attempts to polymerize the guanine-substituted monomer in $\text{CH}_2\text{Cl}_2\text{:MeOH}$ failed to yield any polymer. Thymine-, adenine-, and cytosine-substituted monomers could be polymerized on a small scale to afford polymers with good PDI values (1.1–1.3); however, these polymerizations were not successful above a M:I ratio of 5:1. These results indicate that the synthesis of polymers containing nucleoside bases remains a challenge. With advances in catalyst and alterations in base-protecting groups, perhaps polymers that assemble by base pairing can be generated.

Materials that present single strands of oligonucleotides have been synthesized by using ROMP. Many researchers have utilized polymer/oligonucleotide hybrids as DNA biosensors [70–72]. Although these strategies have proven effective, one potential limitation of these materials is the ill-defined nature of the scaffolds. To address this limitation, Nguyen and coworkers recently published a method for generating polymers by ROMP that contain oligonucleotide strand (Figure 3.6-10) using a post-polymerization modification (see Section 3.6.2.5) approach [73]. They first polymerized a norbornene-based monomer possessing a primary hydroxyl group. Subsequent to the polymerization, the free hydroxyl groups were converted to phosphoramidites under standard conditions and then coupled to oligonucleotides immobilized on control pore glass (CPG). Cleavage of the conjugate from the

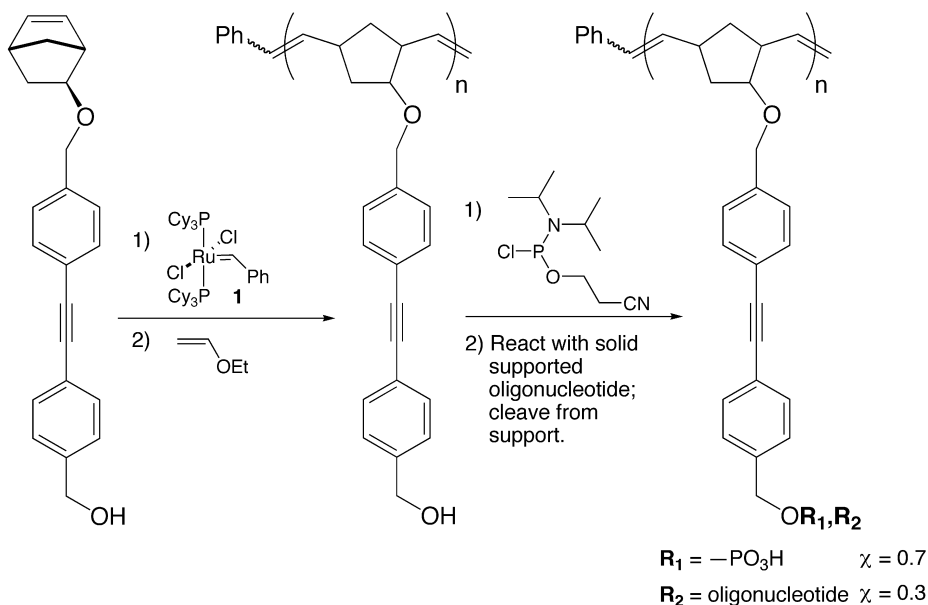


Fig. 3.6-10. Post-polymerization modification approach to the synthesis of oligonucleotide/polymer hybrids used by Nguyen and coworkers. These oligonucleotide-substituted polymers retained the recognition properties of the attached oligonucleotide strands.

solid support and purification via ultrafiltration yielded polymer/oligonucleotide hybrids that contained, on average, five oligonucleotide strands per polymer as determined by UV spectroscopy. Co-incubation of the materials with complementary oligonucleotides led to the formation of a white precipitate. This process was thermally reversible and the hybrids exhibited a normal melting curve. These results indicate that the polymer backbone does not adversely affect nucleic acid hybridization. The authors hypothesize that this technology could be used to construct unique materials with tailored properties.

3.6.2.4

Synthesis of Drug/Polymer Conjugates via ROMP

Drug/polymer conjugates also have been synthesized by ROMP. These conjugates are not designed to specifically mimic a biopolymer; rather, they are envisioned as drug-delivery vehicles or as more potent or selective ligands [74]. One of the first examples of such conjugates came from the laboratories of Gibson and North (Figure 3.6-11A) [75]. An imide-norbornene monomer with an appended β -lactam antibiotic derivative was successfully polymerized with ruthenium initiator **1** to

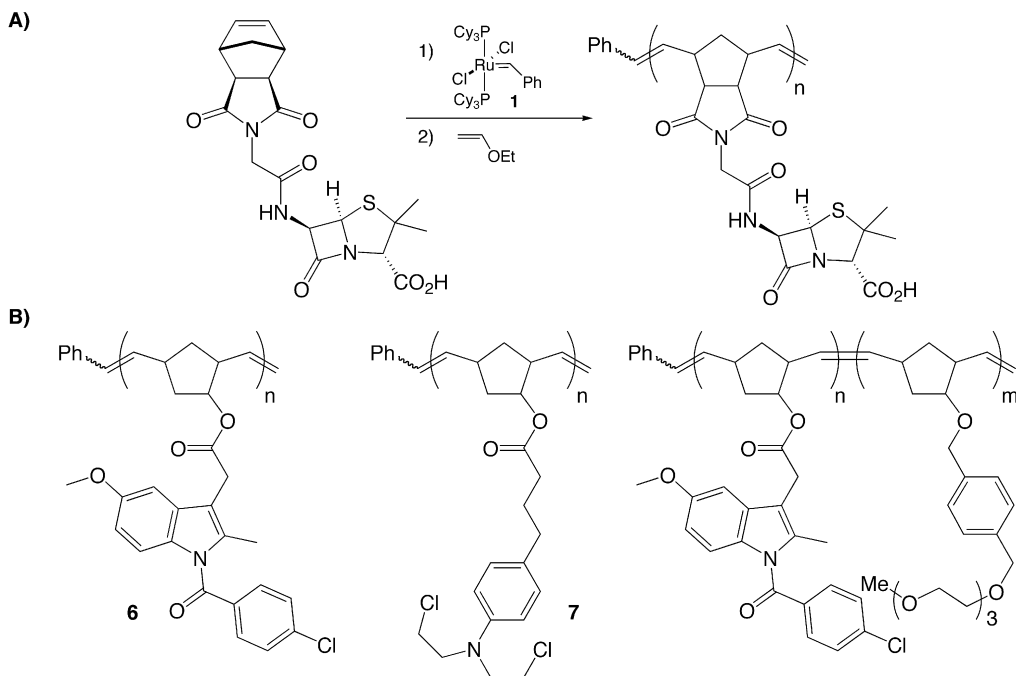


Fig. 3.6-11. Examples of drug/polymer conjugates synthesized via ROMP. (A) Penicillin-substituted polymers synthesized by the Gibson laboratories were the first example

of ROMP-derived drug/polymer conjugates. (B) Nguyen and coworkers have described a similar strategy for the synthesis of polymers containing small molecule anti-cancer agents.

yield short oligomers. Although the solubility of the polymers hampered GPC analysis, it was estimated that they contained 8–17 monomer units along with the intact penicillin ring system. Nguyen and coworkers have also reported the synthesis of ROMP-generated polymers that contain small, drug-like molecules (Figure 3.6-11B) [76]. In these studies, the researchers attached anticancer chemotherapeutics (indomethacin (**6**) or chlorambucil (**7**)) to norbornene-based monomers. Polymerization of either of the two monomers yielded polymers with good PDI values (1.25–1.26). Analogously, a block copolymer of the indomethacin- and ethylene glycol-substituted monomers also was synthesized and found to have a PDI value of 1.2. The authors hypothesize that polymer/drug conjugates synthesized by ROMP will possess pharmacological properties that are distinct from those of other polymer/drug conjugates. For example, the drug dosage could be controlled by manipulating polymer length.

One of the more complex examples of polymer/drug conjugates generated by ROMP is the synthetic oligomers displaying vancomycin derivatives constructed by Arimoto and coworkers (Figure 3.6-12) [77]. This example clearly demonstrates the functional group tolerance of the ruthenium-carbene initiators. Polymerization of the imide-derived monomer conjugated to vancomycin with initiator **1** under emulsion conditions failed to provide an appreciable amount of polymer. However, when the polymerization reaction was conducted in methanol, it proceeded even in the presence of the highly functionalized natural product derivative to give the desired polymer in 60% yield (Figure 3.6-12). Although free amines have been shown to deactivate the catalyst [39], the authors hypothesized that the use of the trifluoroacetic acid salt of vancomycin ameliorated this problem. Purification of the polymer and analysis by polyacrylamide gel electrophoresis indicated that the isolated oligomers contained between 2 and about 15 monomer units. This example highlights the complexity of conjugates that can be generated using ROMP.

3.6.2.5

Post-Polymerization Modification Strategies

Two synthetic challenges common to many of the examples presented above are that the polymer or monomer is often relatively insoluble in the polymerization solvent and that monomers with complex structures can have a deleterious effect on the resulting polymer's PDI value. Many biologically important epitopes have limited solubility in solvents that are compatible with ROMP. Solutions to this problem have included modification of the monomers by introducing protecting or solubilizing groups or alteration of the polymerization conditions (e.g., performing the polymerization under emulsion conditions). Though successful, these approaches are not general, and their application can lead to the production of insoluble polymers or limitations in the length of the polymers that can be synthesized. Furthermore, small changes in the monomer structure can dramatically affect the rates of initiation, propagation, and termination of a given monomer. Thus, each new monomer or ligand utilized may require optimization of the polymerization conditions.

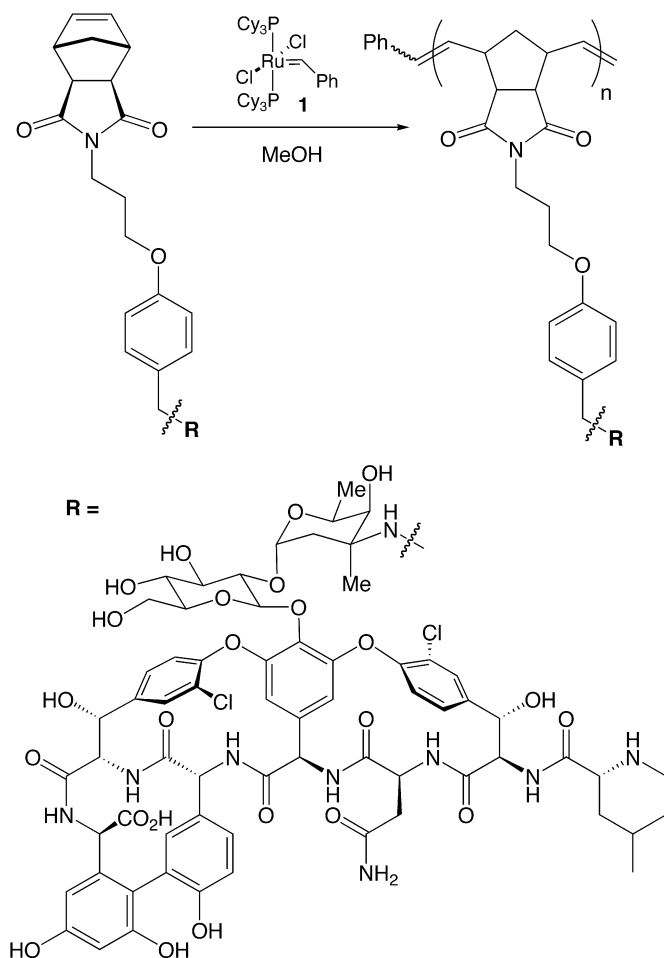


Fig. 3.6-12. Scheme for the synthesis of a polymeric display of the antibiotic vancomycin by ROMP. The functional group tolerance of the ruthenium initiator is illustrated by its ability to polymerize such a highly functionalized monomer.

Recently, another strategy for synthesizing polymers that contain biologically important epitopes using ROMP has been developed. This method does not rely on the polymerization of the epitope as part of the monomer unit. This post-polymerization modification (PPM) strategy utilizes a general monomer unit that contains a reactive functional group that can be modified subsequent to the polymerization [7, 13, 78–81]. By choosing a monomer that yields polymers with good solubility in normal polymerization solvents, the advantages of ROMP can be efficiently exploited to construct materials with defined lengths. Furthermore, by introducing the biological epitope after the polymerization, less-soluble molecules can be conjugated to the polymer in polar solvents such as DMSO or DMF, which

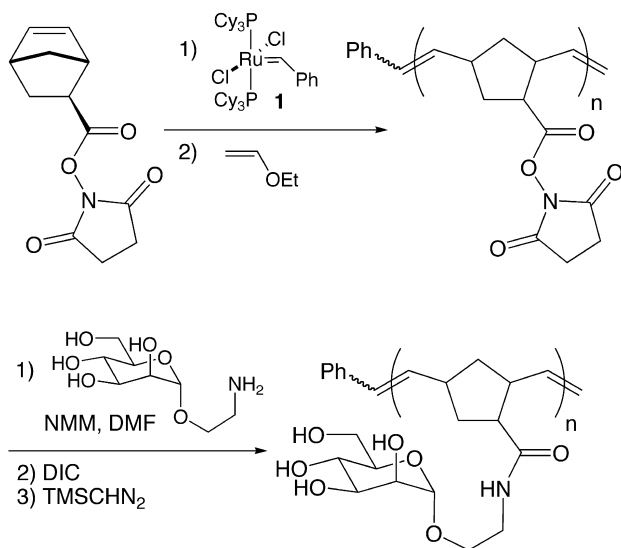


Fig. 3.6-13. Synthesis of bioactive polymers via a post-polymerization modification strategy represents a general approach to these materials. Kiessling and coworkers have described the use of N-hydroxysuccinimide ester-substituted polymers as a general method for attaching amine-bearing ligands to the polymer backbone. The utility of this approach was illustrated by the synthesis of sugar-substituted displays. (NMM = N-methylmorpholine, DIC = diisopropylcarbodiimide, TMS = trimethylsilyl)

are incompatible with the current polymerization catalysts. One example of the PPM method has already been discussed (Section 3.6.2.3) [73], and this strategy was proven to be applicable to the synthesis of DNA/polymer hybrids. Kiessling and coworkers have developed a more general strategy for synthesizing biologically relevant, ROMP-derived polymers by PPM [82]. Polymerization of a monomer that contains an N-hydroxysuccinimide (NHS) ester yields a polymer that can be derivatized with any amine-bearing ligand (Figure 3.6-13). As a proof of concept, the authors derivatized the polymers with an amine-functionalized mannose epitope and compared the resulting polymers to analogous polymers generated using emulsion conditions. Characterization of the materials synthesized by GPC indicated that the polymerization of the activated monomer was living and that the PPM method was more successful at producing longer length polymers than the emulsion conditions. Furthermore, NMR analysis suggested that both polymers presented equivalent amounts of their carbohydrate-recognition epitope, indicating that efficient conjugation of the ligands to the polymer backbone occurs. The authors then compared the biological activity of the polymers synthesized by PPM or emulsion; both types of polymers had similar activities. The polymers generated by PPM were slightly more potent due to their higher average length. These results suggest that polymers derived from PPM are equivalent or superior to those generated under emulsion conditions. To date, most applications of this strategy have been used to synthesize carbohydrate-substituted polymers. However, the reactivity

and chemoselectivity of the activated esters suggest that other ligands such as peptides or small, drug-like molecules could also efficiently be attached to the polymer backbone [83, 84]. The PPM strategy should facilitate the rapid synthesis of new polymeric ligands and alleviate many of the problems encountered in the previous examples.

3.6.2.6

End-Capping Strategies

In addition to the advantages of ROMP previously described, the living nature of the polymerization also provides a novel method to attach reporter groups to polymers. The resulting materials can be used to probe biological systems. Compounds that contain reporter groups such as fluorophores or biotin groups are particularly useful for directly visualizing and quantitating binding events. For polymeric ligands, such reporter moieties are typically introduced through the polymerization of a fluorophore-substituted monomer or through random conjugation to the polymer backbone via PPM [7, 13, 85]. Although useful for many purposes, these strategies provide limited control over the number and location of the introduced functionality. However, polymers synthesized via ROMP can be functionalized in a defined manner by utilizing the catalytically active metal center of the propagating intermediate for further transformations. Treatment of the metal carbene with either an aldehyde for the molybdenum-carbene initiators or an electron-rich olefin for the ruthenium-carbene initiators terminates the polymerization and generates materials with a defined end group (Figure 3.6-2) [34–38]. The use of an appropriately functionalized terminating agent provides polymers with a discrete attachment point that can be used to incorporate a single reporter group.

Schrock and coworkers have utilized functionalized aldehydes to provide materials with unique redox and luminescence properties (Figure 3.6-14). In their initial

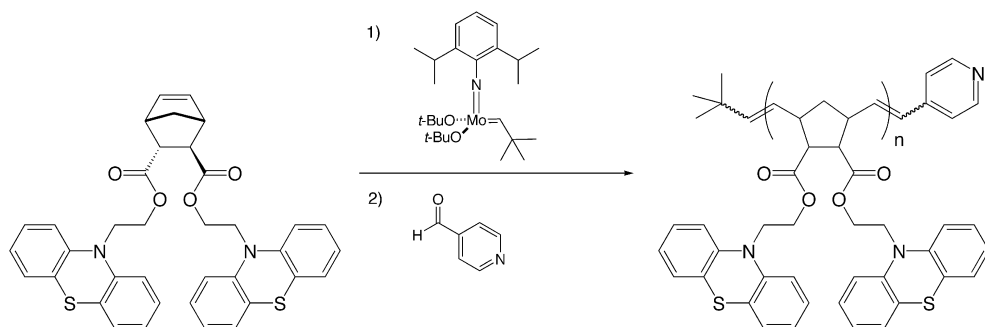


Fig. 3.6-14. Specific end labeling of polymers containing terminal molybdenum carbenes can be accomplished via termination of the reaction with a functionalized aldehyde. In one

application of this strategy, Schrock and coworkers synthesized end-functionalized materials that could be attached to the surface of an electrode in a defined manner.

studies [35], they demonstrated that polymers terminated with 4-pyridine-carboxaldehyde reacted with electrodes derivatized with (*p*-(chloromethyl)phenyl)-trichlorosilane to yield a polymer-coated electrode with altered electrochemical properties. Their second example explored the effects of different backbone substituents on the luminescence of a single pyrene unit attached at the polymer termini via end labeling [34]. Although these examples demonstrate the potential utility of end-capping strategies, the molybdenum initiators are not as tolerant of many functional groups present in biologically active epitopes.

To address this issue, two groups have explored strategies for end-labeling materials generated by ruthenium-initiated ROMP. Kiessling and coworkers explored the synthesis of end-labeled materials via functionalized enol ethers. In their initial studies [37], an ethyleneglycol-based capping agent that contains a protected acid was used to terminate polymerizations conducted under emulsion conditions (Figure 3.6-15). The terminal ester group could be hydrolyzed under basic conditions, and fluorescein cadaverine conjugated to the resulting acid. However, the yield of end-capped polymers obtained was low (30%) due to competing termination events. In contrast, when the polymers were generated under PPM conditions, the capping efficiencies improved to approximately 80%. Based upon this success, Kiessling and coworkers subsequently developed a second generation of capping agents that possess a wider range of functional groups [36]. These enol ethers result in efficient termination under homogeneous polymerization conditions to afford polymers with unique end groups. Through these unique end groups, fluorescent reporter groups could be introduced or the polymers could be attached to surfaces [86].

Molecular oxygen has also been used to terminate ROMP to yield materials that contain a terminal aldehyde (Figure 3.6-16) [61]. Gibson and coworkers initially noticed these termination events in their analysis of mass spectrometry data from thymine-containing polymers (Section 3.6.2.3) [68]. They explored this reaction in an approach to the synthesis of end-modified, amino acid-containing polymers [61]. Exposure of the polymerization reaction to oxygen resulted in efficient generation of an aldehyde group at the polymer termini. This aldehyde functionality could then be reduced to the alcohol or oxidized to the carboxylic acid. Polymers possessing carbohydrate residues have also been end labeled using molecular oxygen [87]. The resulting compounds could be reacted with a hydrazine-containing fluorescein derivative to yield polymers that contain a single fluorophore. Thus, defined metal-carbene initiators can facilitate the synthesis of specifically end-labeled multivalent ligands.

From the preceding examples, it is clear that ROMP is well suited for the synthesis of polymeric displays of bioactive compounds. In particular, the compatibility of the polymerization reaction with polar functional groups is advantageous for the incorporation of biologically relevant functionality. Each of the examples demonstrate the advantages of ROMP catalyzed by initiators such as **1** or **2**; however, the utility of ROMP for the synthesis of biologically relevant displays is highlighted when the resulting materials are applied to the study of biological systems. We

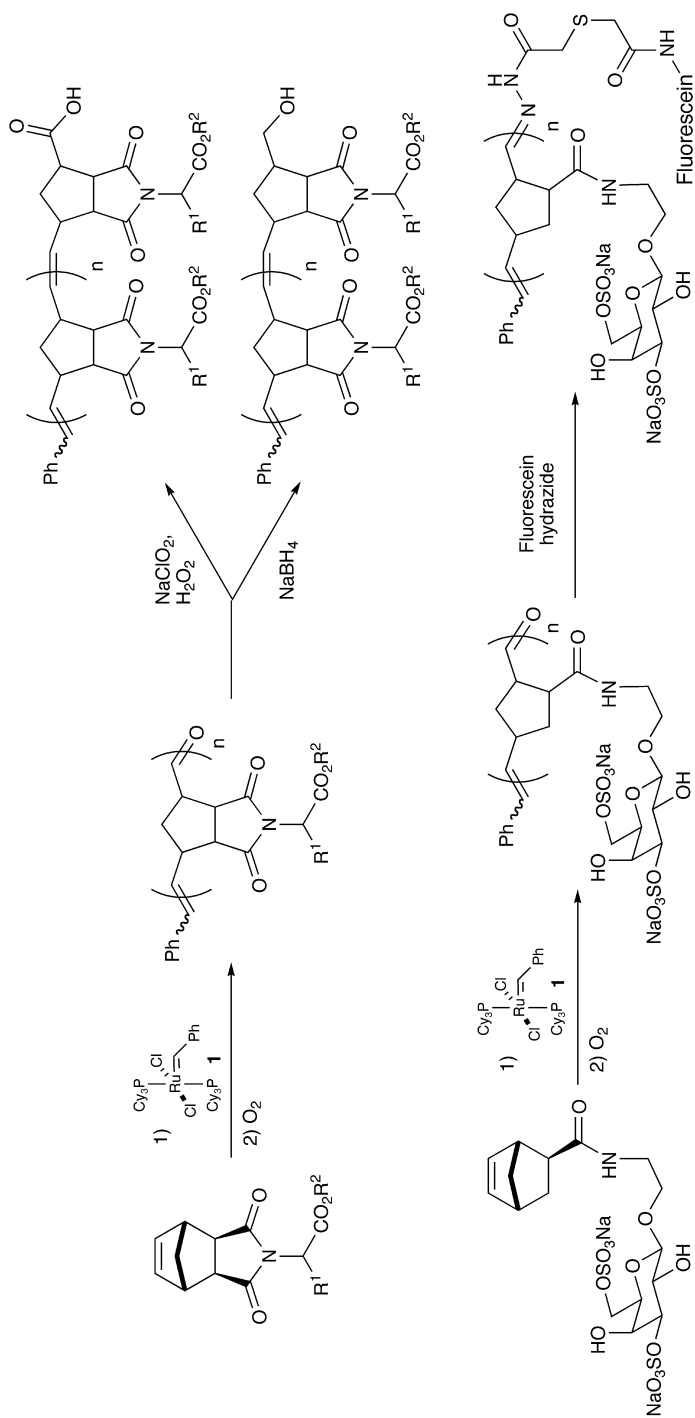


Fig. 3.6-16. Example of the termination of ruthenium carbene-initiated polymerizations with molecular oxygen. The reaction leads to a polymer with a terminal aldehyde functional group that can be manipulated via subsequent transformations.

3.6.3

Applications of Biologically Active Polymeric Displays

3.6.3.1

Protein-Carbohydrate Interactions

Protein-carbohydrate interactions play important roles in a wide range of biological processes, including host-pathogen recognition, the immune response, inflammation, and fertilization [1, 2, 88–90]. Unlike many receptor-ligand interactions, however, the binding affinity of a carbohydrate-binding protein (lectin) for a single carbohydrate epitope is generally weak ($K_d \approx 10^{-3}$ – 10^{-4} M). Many lectins bind to a range of saccharide epitopes with similar affinities [91]. To control the avidity and specificity of protein-carbohydrate interactions, nature relies on multivalent displays. Examples include highly glycosylated proteins and glycolipid assemblies. It is hypothesized that these multivalent displays are important in mediating specific and avid protein-carbohydrate interactions [3, 92]. In many cases, the naturally occurring ligands involved in these processes are either difficult to isolate or are too heterogeneous to be used effectively in mechanistic studies. Consequently, synthetic, multivalent displays of carbohydrates that mimic these naturally occurring displays are valuable tools for probing protein-carbohydrate interactions.

Since the pioneering work by Y. C. Lee on the cluster glycoside effect [91, 93], researchers have explored a wide range of synthetic scaffolds for displaying carbohydrate epitopes, including small molecules, dendrimers, and polymers [8, 10]. Each of these scaffolds has been used to develop potent ligands for a range of different lectins [94–99]. Each of these scaffolds, therefore, has an important place in the study of protein-carbohydrate interactions, yet ligands generated by living polymerization reactions have several advantages. One benefit of living polymerization reactions is that materials of different valencies can be synthesized quickly, from short oligomers to materials of high valency. In contrast, small molecule and dendrimer scaffolds are limited in the number of epitopes they can display and in the distances they can span. Interestingly, polymers generated by ROMP are more effective at promoting receptor clustering than are other scaffolds [100]. This ability to cluster proteins can affect both the strength of the protein-ligand interaction and the biological consequence of that interaction. As a result, materials generated by ROMP have found particular utility in probing protein-carbohydrate interactions.

ROMP-generated polymers as tools for the development of rationally designed multivalent ligands One key advantage of using synthetic ligands to investigate protein-carbohydrate interactions is that the effect of ligand structure on an observed activity, such as a binding affinity or biological outcome, can be determined. Despite this advantage, interpreting these relationships is complicated because multivalent ligands can engage in a range of different binding modes (Figure 3.6-17) [1, 3]. These include the chelate effect, the statistical effect, receptor clustering, subsite binding, and steric stabilization. The ability of the ligand to utilize

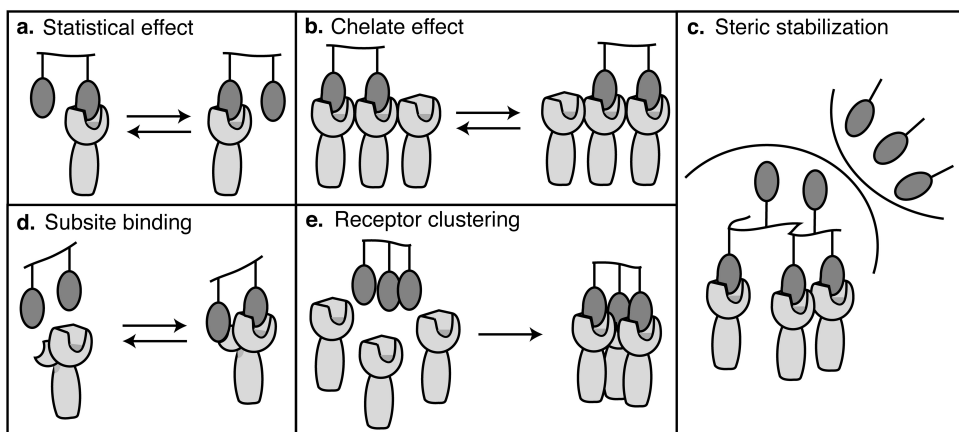
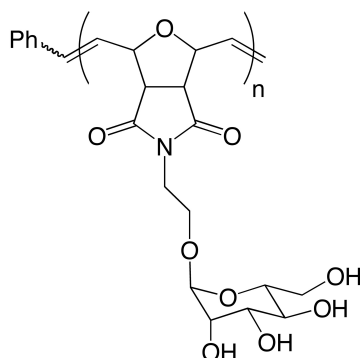


Fig. 3.6-17. Binding modes available to multivalent ligands. (A) Statistical effect. Multivalent presentation increases the effective local concentration of the ligand and promotes rebinding of the ligand to the receptor. (B) Chelate effect. Simultaneous binding of multiple receptors by multiple ligands decreases the rate of ligand dissociation and increases ligand affinity. (C) Steric stabilization. The steric bulk of a bound multivalent ligand

precludes binding of additional ligands. (D) Subsite binding. Multivalent ligands bind to a primary and secondary binding site contained on the same receptor. (E) Receptor clustering. Multivalent ligand binding alters the proximity or orientation of the liganded receptors. This binding mode can result in increased avidity through favorable protein-protein interactions and/or the induction of signaling events.

these mechanisms depends upon the structure of both the multivalent ligand and the receptor of interest [100, 101]. Variables such as the valency of the display, the density and orientation of the displayed epitopes, the distance between those epitopes, and the distance between receptor binding sites may all affect how a ligand interacts with its receptor. Furthermore, multivalent ligands rarely utilize a single binding mechanism. For example, ligands that act via the chelate effect may also be able to cluster receptors under the appropriate conditions. Because ligand features can be varied using ROMP, the activities of the compounds that result can be optimized for the desired activity.

Although it is relatively simple to compare ligands on the basis of potency, it is difficult to deconvolute the relative contributions of each of these binding modes to the observed avidities. Kiessling and coworkers explored the effect of polymer valency on ligand potency [56, 102]. Although it was known that multivalent displays of carbohydrates can be more potent inhibitors, the effect of polymer valency on binding avidity had not been systematically explored. For these studies, the authors chose the well-characterized, tetrameric, mannose-binding lectin concanavalin A (Con A) [103] as their target lectin. The authors assessed the ability of various mannose-substituted polymers (Figure 3.6-18) to bind to Con A using two competitive-binding assays. From these studies, the authors found that the potency of the polymers on a saccharide residue basis was increased with increasing valency and that above a certain length, the potency of these polymers reached



Degree of Polymerization	Relative Potency
monomer	1
10	100
25	300
52	2000
143	2500

Fig. 3.6-18. Inhibitory potency of mannose-substituted polymers generated by ROMP was determined in a cell agglutination assay using the lectin Con A. The potency of the mannose-substituted polymers depends on their valency.

The potency of each compound reflects the ability of these compounds to inhibit Con A-mediated aggregation of red blood cells (hemagglutination) and is relative to α -methyl mannose [56].

a plateau. These increases in binding avidity relative to the monovalent ligand (α -methyl mannopyranoside (α MeMan)) most likely result from contributions from different binding modes (Figure 3.6-17). Molecular modeling experiments suggest that the polymer with a DP of 10 is too short simultaneously place two mannose binding epitopes in two binding sites on a single Con A tetramer. Still, these materials are significantly more potent than the corresponding monosaccharide. The authors hypothesized that the observed potency could result from intermolecular clustering/cross-linking of multiple Con A tetramers. Subsequent studies support this hypothesis [100, 104]. Furthermore, as the length of the polymers increases, so does their ability to inhibit Con A-mediated agglutination. These results point to the importance of polymer valency in controlling ligand potency.

In principle, multivalent displays that present the same ligand could act as either an effector (i.e., promotes receptor clustering) or an inhibitor (i.e., binds with high functional affinity) (Figure 3.6-19). Furthermore, the structure of a multivalent ligand can influence the kinetics with which it clusters a target receptor as well as the ultimate size of the cluster formed. These differences also can impact how effectively a signal is transmitted [3]. Most importantly, elucidating the relationship between structure and function can lead to insight into what structural features give rise to ligands that act by a specific mechanism or elicit a specific biological response.

To explore how a ligand's structure influences its mechanism of action, Gętwicki et al. synthesized a series of diverse ligands and assessed their interaction with a single protein using four different assays [100, 101]. The goal of these studies was to investigate how the architecture of a ligand influences its ability to inhibit or cluster receptors. Specific aspects of ligand-promoted clustering were tested, including the rate of cluster formation, the size of the cluster, and the distance between the individual receptors within a cluster. The target protein

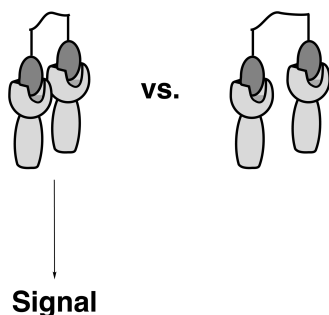
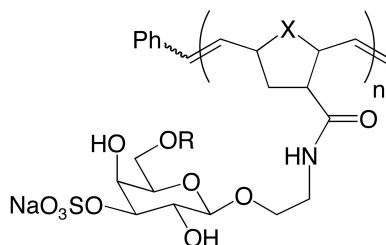


Fig. 3.6-19. One example of the effect of ligand structure on receptor clustering. On the right, the multivalent ligand interacts with a dimeric receptor by the chelate effect. On the left, the multivalent ligand preferentially clusters the dimeric receptor.

employed was the mannose-binding lectin Con A. The ligands tested included a series of polymers generated by ROMP that differed in their degree of polymerization and in the density (mole fraction) of mannose epitopes presented. Other multivalent scaffolds were also tested, including small molecules, ligand-conjugated proteins, dendrimers, and polydisperse polymers (polyethylene maleic anhydride-substituted polymers). Compared to the other ligands, the polymers generated by ROMP are especially well suited for controlling various aspects of receptor clustering. Specifically, they were superior to the other ligands tested at rapidly clustering receptors. They were also most effective at bringing receptors into close proximity. Because the kinetics of receptor clustering is critical for transducing signals and because receptor proximity also influences signal generation, polymers generated by ROMP should be useful tools for probing the role of receptor clustering [54, 105–109] in signal transduction.

The selectins and the inflammatory response Polymers generated by ROMP that display sulfated carbohydrates have been used to explore the role of multivalent protein-carbohydrate interactions in the inflammatory response. During inflammation, white blood cells interact with the endothelial cells that line the blood vessel wall, which leads to leukocyte recruitment to a site of injury. These cell interactions are mediated by the selectin family of C-type lectins (E-, L- and P-selectin) [110, 111]. E-selectin and P-selectin are both found on endothelial cells and are produced in response to inflammatory signals, but L-selectin is constitutively displayed on leukocytes [112]. Complementary ligands for the selectins exist on both endothelial cells and on leukocytes. These include the glycoproteins (e.g., GlyCAM-1 and PSGL-1) that display multiple copies of sulfated carbohydrate residues, including the tetrasaccharide sialyl Lewis^x (sLe^x) [113–115]. P- and L-selectin have also been found to bind to sulfated glycolipids such as the sulfatides [116, 117], which form multivalent displays. Thus, multivalent binding may be important for selectin-mediated cell-cell interactions.

Researchers have sought to develop methods for inhibiting inflammation by blocking selectin-ligand interactions [118]. One possible strategy for inhibiting selectin-ligand interactions is to utilize synthetic materials that mimic the naturally occurring carbohydrate displays that the selectins bind. Kiessling and coworkers hypothesized that polymers generated by ROMP that displayed a sulfated galactose derivative could be used to mimic glycolipid displays formed by sulfatides [52, 53]. To this end, polymers displaying 3-sulfo or 3,6-disulfogalactose residues were generated under homogenous and emulsion conditions (see “Polymerization of unprotected sugar epitopes with defined initiators” section). The ability of the resulting materials to inhibit the binding of HL60 cells (a leukocytic cell line) to purified protein (Figure 3.6-20) was tested. For the polymers synthesized under



i)

Compound	P-selectin IC ₅₀ (mM)	L-selectin IC ₅₀ (mM)	E-selectin IC ₅₀ (mM)
sLe ^x	3.4 ± 0.27	3.5 ± 0.18	3.3 ± 0.17
X=O, R = H	2.2	75% @ 3.0	2.9
X = O, R = SO ₃ Na	0.084	1.7	90 @ 0.17

ii)

Compound	P-selectin IC ₅₀ (mM)	L-selectin IC ₅₀ (mM)	E-selectin IC ₅₀ (mM)
X = O, R = H	7.8	0% @ 20.0	20
X = CH ₂ , R = H	1.2	0% @ 20.0	0% @ 20.0
X = O, R = SO ₃ Na	13% @ 20.0	13% @ 20.0	13% @ 20.0
X = CH ₂ , R = SO ₃ Na	0.17	18	58% @ 20.0

Fig. 3.6-20. ROMP was used to generate polymers displaying sulfated galactose derivatives. These compounds, which were designed to function as glycolipid mimics, act as inhibitors of selectin-ligand interactions. The ability of these polymers to inhibit the

binding of HL60 cells to immobilized protein is reported as the concentration of saccharide residues that afford 50% inhibition of binding (IC₅₀ value) [52]. In those cases in which IC₅₀ values were not available, the percent inhibition at a particular concentration is reported.

homogenous conditions, the monosulfated polymers were approximately as potent as monomeric sLe^x . However, the polymers substituted with 3,6-disulfogalactose residues were 40-fold more potent at inhibiting P-selectin than was sLe^x on a saccharide residue basis. In addition, this polymer exhibited a 20-fold preference for P- over L-selectin. Interestingly, the polymers synthesized under emulsion conditions were less potent than those generated using homogeneous conditions. The authors hypothesized that, for these highly charged monomers, the homogeneous polymerization conditions yielded polymers with broader molecular weight distribution. High-molecular-weight polymers are likely to be extremely potent inhibitors.

Inhibitors of selectin-ligand interactions that function under physiological flow conditions (such as those found in the blood) also have been generated using ROMP [55]. As previously mentioned, sulfation of the sLe^x epitopes presented by glycoproteins is critical for L-selectin binding activity [114]. To address how carbohydrate sulfation influences activity, two polymers that present different sulfated derivatives of the Lewis^x trisaccharide were synthesized using ROMP (Figure 3.6-21). Both polymers exhibited similar affinities for L-selectin in a static,

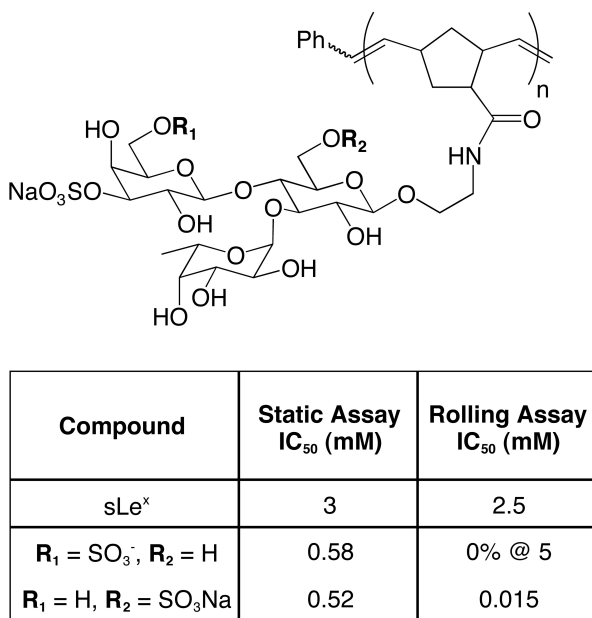


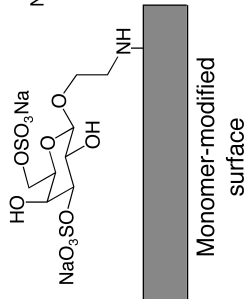
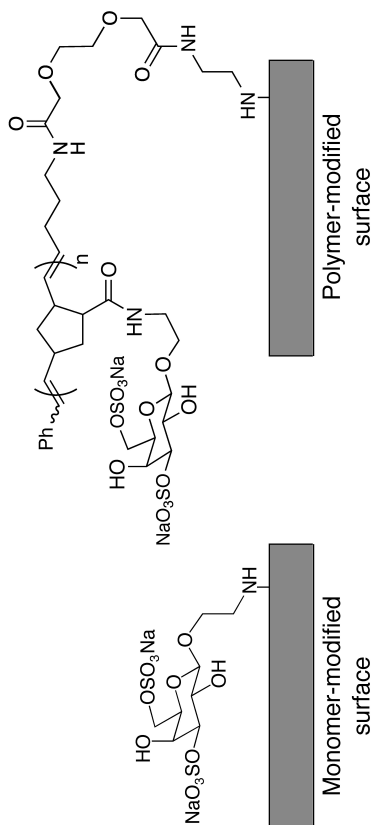
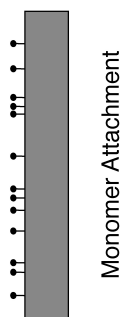
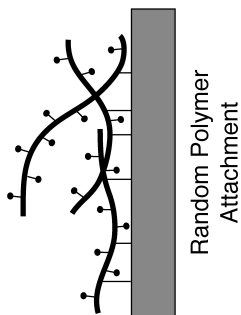
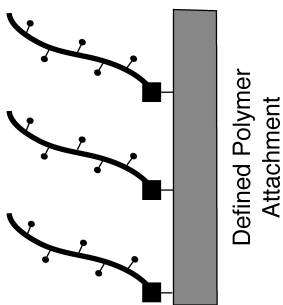
Fig. 3.6-21. Mimics of glycoproteins that display sulfated carbohydrates were generated using ROMP. Differences between the inhibitory potency of the two polymers under static and dynamic conditions were identified. For the static assay, the IC₅₀ values reflect the ability of reported polymers to inhibit the

binding of purified L-selectin to heparin [55]. IC₅₀ values reported for the rolling assay were determined by measuring the ability the ligands to inhibit the rolling of cells displaying L-selectin on a glycoprotein (GlyCAM-1)-coated surface under conditions of shear flow.

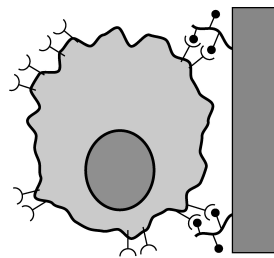
cell-free binding assay. However, these static conditions do not effectively mimic the forces that leukocytes encounter in the bloodstream. The ability of the polymers to inhibit L-selectin-mediated rolling of cells on immobilized GlyCAM-1 under conditions of shear flow was therefore examined. The polymer displaying 3',6-disulfo Le^x effectively inhibited rolling with a concentration that afforded 50% inhibition (IC₅₀ value) of 15 μM, but the polymer containing 3',6'-disulfo Le^x had no activity even at high concentrations (5 mM). These results demonstrate that ligands generated by ROMP can have very potent activities for medically relevant protein targets.

Ligands for the selectins generated by ruthenium carbene-initiated ROMP also have been used to generate surfaces for investigating biological interactions [86]. Gestwicki et al. modified a gold surface with selectin ligands generated by ROMP to measure selectin-ligand interactions using surface plasmon resonance (SPR) experiments. A bifunctional capping agent (Section 3.6.2.6) was used to introduce a functional group at the polymer terminus, providing a means to specifically attach their ROMP-generated polymers to a surface. SPR experiments indicate that soluble P- and L-selectin bind to these surfaces. Cells that display L-selectin also bind (Figure 3.6-22). It is hypothesized that specific attachment of the polymers to a surface provides a more accurate mimic of glycoprotein ligands than do surfaces derivatized using a less selective immobilization reaction. Both this study and the previous example focused on the inhibition of cell rolling demonstrate how ligands generated using ROMP can be used to probe structure-activity relationships of multivalent ligands.

The sulfated, polymeric ligands generated by ROMP also can be used to modulate the levels of L-selectin displayed on the surface of white blood cells. Treatment of neutrophils with polymeric but not monomeric 3',6-disulfo Le^x resulted in the loss of L-selectin from the cell surface [54]. Similar results were obtained with polymeric displays of 3,6-disulfogalactose [51]. L-Selectin can be constitutively shed (or proteolytically released) from the cell surface [119], and other compounds, such as phorbol esters, are also known to induce L-selectin release [120]. The authors suggest that polymer- and phorbol ester-induced shedding proceeds via different mechanisms. Polymer-mediated shedding appears to occur independent of cellular activation and presumably results from ligand-induced clustering of multiple copies of L-selectin on the cell surface (Figure 3.6-23). Additional evidence for the clustering hypothesis has been obtained. ROMP-generated polymers substituted with 3,6-disulfogalactose residue that contain a single fluorescent reporter group (see Section 3.6.2.6) bind specifically to L-selectin positive cells [37]. Using ligands varying in degree of polymerization (DP), a fluorescence-based cell assay was used to assess the binding avidity of the polymers for cells displaying L-selectin [36]. The longer polymers bound with higher avidity than did the shorter ligands. In addition, the polymers of higher DP gave a weaker maximal fluorescence intensity signal at saturating concentrations of ligand than did the polymers of lower DP. The finding that the fluorescence intensity varied inversely with the valency of the ligand (Figure 3.6-23) suggests that the polymers interact with multiple copies of L-selectin. Thus, the number of copies of cell surface L-selectin that interact with



Surface	P-selectin K_d (μM)	L-selectin K_d (μM)
Monomer	7.7 ± 0.4	2.0 ± 0.2
Polymer	1.5 ± 0.1	0.3 ± 0.02



A)

B)

C)

the polymers depends on the valency of the ligand. These studies suggest that the polymers cluster L-selectin. Moreover, they underscore the power of ligands generated by ROMP for understanding the role of multivalency in a complex biological system.

3.6.3.2

Integrins and Cellular Adhesion

Members of the integrin family of cell-adhesion proteins play a critical role in cellular adhesion, proliferation, and trafficking as well as in pathological processes such as tumor cell invasion and inflammation [121–124]. Many integrins bind to the peptide motif Arg-Gly-Asp (RGD) found on extracellular matrix proteins such as fibronectin and vitronectin. As a result, many researchers have focused on developing RGD-based inhibitors that block the interactions between an integrin and its ligand [125, 126]. Grubbs and coworkers recently described the use of ROMP [64, 65] to generate a series of polymers that contain both a Gly-Arg-Gly-Asp-Ser (GRGDS) motif and a peptide sequence, Pro-His-Ser-Arg-Gln (PHSRN) [127]. The latter sequence is suggested to bind synergistically with the RGD motif. The authors hypothesized that the resulting multivalent ligands would be more potent inhibitors of fibroblast adhesion than would the monovalent peptide. To test this hypothesis, fibroblasts were treated with the monovalent peptide GRGDS and the polymeric GRGDS, and the ability of these compounds to inhibit cell adhesion to fibronectin-coated surfaces was assessed (Figure 3.6-24). The IC_{50} values determined from these experiments are 1.33 and 0.18 mM for the monovalent and multivalent inhibitors, respectively (the value for the multivalent ligand is reported on a peptide sequence basis). This increase in inhibitory potency appears to be a result of the multivalent presentation of the RGD epitope. Treatment with a polymer displaying the peptide Gly-Arg-Gly-Glu-Ser (GRGES), which binds with low affinity to integrins, resulted in no significant inhibition of adhesion. Furthermore, treatment with a random copolymer displaying both GRGDS and PHSRN sequences yielded an even more potent inhibitor with an IC_{50} value of 0.040 mM, 33-fold more potent than the monovalent peptide (GRGDS). These experiments suggest that materials synthesized using ROMP may function as a new class of integrin modulators.

← **Fig. 3.6-22.** Polymers displaying sulfated galactose residues were generated using ROMP. The polymerization was terminated with a functionalized enol ether, which could be derivatized to allow surface attachment (A and B). The resulting surfaces were tested in selectin-binding assays using surface plasmon resonance. (A) Specific attachment of polymeric ligands more closely mimics the biological presentation of carbohydrate epitopes on glycoproteins. (B) Surfaces

derivatized with a monovalent or multivalent ligand show different binding affinities for P- and L-selectin. The apparent K_d values for each compound were determined by fitting SPR response curves determined at different ligand concentrations using BIAevaluation software. A 1:1 binding model was employed [86]. (C) Polymer-functionalized surfaces support the attachment of fluorescently labeled cells displaying the protein L-selectin as visualized by fluorescent microscopy.



3.6.3.3

Pathogenic Organisms

ROMP also has been used to synthesize novel antibiotics. These studies were directed at antibiotic-resistant organisms. The appearance of new strains of antibiotic-resistant organisms constitutes one of the major health-related challenges facing the world today [128–130]. For example, resistance to vancomycin, one of the last lines of defense against many pathogenic organisms, has emerged in the highly pathogenic, methicillin-resistant *Staphylococcus aureus* (MRSA) [131, 132]. As a result, researchers have sought to develop new classes of antibiotics and new methods for delivering known antibiotics to improve their potency and efficacy. Vancomycin inhibits cross-linking of the bacterial peptidoglycan by binding to the terminal D-Ala-D-Ala residues of the mucopeptide precursors [133]. Resistance to vancomycin occurs from the activation of a series of proteins that generate and utilize D-Ala-D-Lac instead of D-Ala-D-Ala for peptidoglycan biosynthesis [134, 135]. This alteration of the bacterial biosynthetic machinery decreases the potency of vancomycin by 100- to 1000-fold. Studies had suggested that covalent and non-covalent dimerization of vancomycin might influence its antibacterial activity. For example, vancomycin dimers exhibit increased activity against vancomycin-resistant *Enterococci* (VRE) [133, 136, 137]. Based on these results, Arimoto and coworkers hypothesized that a polymeric display of vancomycin would exhibit increased binding to the D-Ala-D-Lac residues and lead to the generation of a viable antibiotic for treating vancomycin-resistant organisms.

Using ROMP, the authors generated a polymer that presents 2–15 copies of vancomycin, and the activity of the resulting materials was tested against vancomycin-resistant organisms [77]. The vancomycin-substituted polymer exhibited a 60-fold increase in potency over monomeric vancomycin against VRE (Figure 3.6-25). Interestingly, this polymer was approximately 10-fold less effective against MRSA than either vancomycin or the vancomycin-substituted monomer.

To explore the mechanism of action of the polymer, Arimoto and coworkers determined its apparent dissociation constant for surfaces derivatized with either

← **Fig. 3.6-23.** Polymers that display sulfated carbohydrate residues induce shedding (proteolytic release) of L-selectin from the cell surface [54]. (A) A model for polymer-induced shedding of L-selectin. The multivalent ligands may facilitate receptor clustering, which leads to protease activation and subsequent cleavage of the receptor. (B) Using multivalent ligands containing a single fluorophore, Kiessling and coworkers were able to demonstrate that longer polymers are able to simultaneously interact with multiple copies of L-selectin. For these assays, Jurkat cells (a T-lymphocyte-derived cell line) were treated with varying

concentrations of fluorescein-labeled ligand; the amount of bound ligand was quantitated by the fluorescence-emission intensity of the sample. Apparent K_d values were determined from plots of fluorescence intensity versus saccharide residue concentration. The calculated stoichiometry is defined as the number of copies of L-selectin that interact simultaneously with a polymer of a given DP. This information was determined from the maximal fluorescent signal of each ligand and the total number of copies of L-selectin that are present on the cell surface [36].

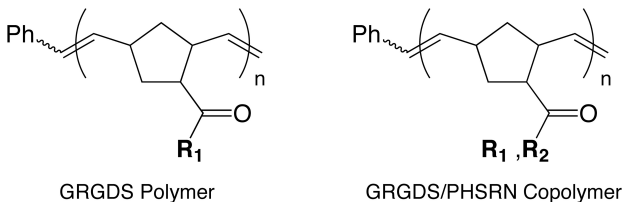


Fig. 3.6-24. Polymeric displays that present the integrin-binding motif, RGD, and the fibronectin synergy sequence, PHSRN, were synthesized by ROMP. The polymers are more effective inhibitors of fibroblast adhesion than

D-Ala-D-Ala or D-Ala-D-Lac [138]. The polymer exhibited about a 10-fold increase in binding over monomeric vancomycin to the D-Ala-D-Ala-substituted surface ($K_d = 2.8 \times 10^{-6}$ M). For the D-Ala-D-Lac surface, no observable binding was detected for monomeric vancomycin. The polymer had an apparent K_d of 2.0×10^{-5} M. The ability of the polymer to bind to the D-Ala-D-Lac-substituted surface

MIC/ μ g mL⁻¹

Compound	<i>S. aureus</i>	<i>Enterococcus</i>	VRE (Van A)	VRE (Van B)
VCN	0.2	<0.5	>250	125
Monomer	0.2	<0.5	>250	125
Polymer	2.3	2	31	2

K_d (M)

Compound	D-Ala-D-Ala Surface	D-Ala-D-Lac Surface
VCN	3.25 X 10 ⁻⁵	no binding
Monomer	4.65 X 10 ⁻⁵	no binding
Polymer	2.83 X 10 ⁻⁶	2.00 X 10 ⁻⁵

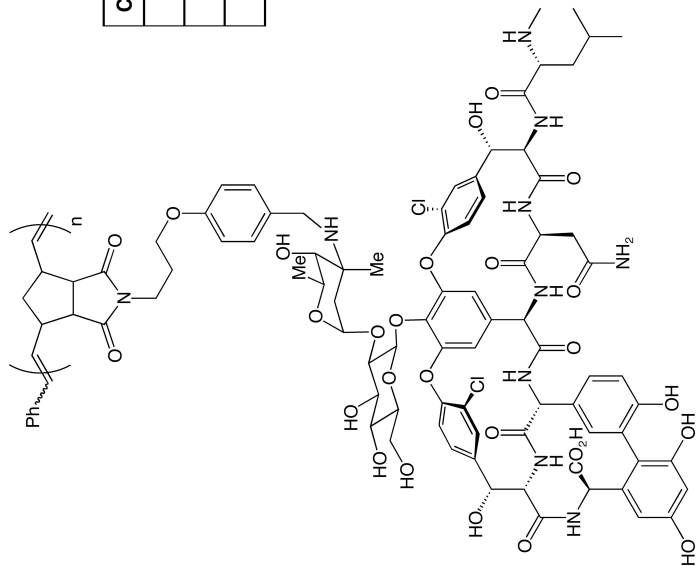


Fig. 3.6-25. Polymeric displays of vancomycin exhibit increased potency against vancomycin-resistant *Enterococci* (VRE). The authors hypothesize that this increase in potency is due to increased functional affinity of the multivalent display for the D-Ala-D-Lac epitopes found in the cell walls of resistant bacteria, but the precise mechanism is not

clear. The reported minimum inhibitory concentration (MIC) values represent the minimum concentration of compound required to completely inhibit the growth of the targeted bacterium [77]. The equilibrium dissociation constant (K_d) values were determined by analysis of SPR-derived sensorgrams at various concentrations of ligand [138].

and its enhanced binding to the D-Ala-D-Ala-substituted surface could explain its increased potency against VRE. The data, however, do not explain the observed decrease in potency against MRSA. Thus, more research will be required to understand the mechanism of action of the vancomycin-substituted polymers. Still, these results highlight the potential benefits of multivalent ligands.

3.6.3.4

Cell Clustering

Polymers synthesized using ROMP have also been found to promote cell-cell clustering or aggregation [139]. It was hypothesized that mannose-substituted polymers could be used to form soluble clusters of the protein Con A and that these clusters could bind to cell surface glycoproteins and thereby aggregate cells. Treatment of Jurkat cells with polymer alone did not lead to cell aggregation (Figure 3.6-26); however, treatment of Jurkat cells with Con A premixed with a polymer of DP = 142 resulted in an increase in cell aggregation over treatment with Con A alone. The increase in aggregation is postulated to be due to the increased avidity of clustered Con A for eukaryotic cell surfaces that display many glycoproteins (Figure 3.6-26). These results suggest that polymers generated by ROMP could be used to cluster cells through either covalent or non-covalent association of proteins with the polymer backbone. The ROMP-derived materials may have potential as reagents for clearing pathogenic organisms from the bloodstream [140, 141].

3.6.3.5

Bacterial Chemotaxis

In most of the examples reviewed in this chapter, ligands generated by ROMP have been used as inhibitors of a particular interaction. However, ROMP-derived ligands also have been used as effectors of specific responses. To this end, they have been used as attractants in bacterial chemotaxis.

The ability of a cell to sense and respond to extracellular signals is essential for its function and survival. Researchers have utilized bacterial chemotaxis as a model system to study these sensing and signal transductions [142–145]. *Escherichia coli* utilize four primary ligand-binding membrane-bound chemoreceptors, Tsr, Tar, Tap, and Trg, to sense and respond to a range of attractants including serine, aspartate, dipeptides, and galactose/ribose, respectively. Upon binding their respective ligands, these receptors initiate a signaling process that ultimately controls the locomotion of the bacteria either towards or away from the ligand. One remarkable feature of this chemosensory system is that bacteria have the ability to sense small changes in the amount of a chemoattractant over a broad range of concentrations. *E. coli* can sense chemoattractant changes of less than 5% over a concentration range that spans 6 orders of magnitude [146]. However, the mechanistic basis of this sensitivity is not well understood. A mathematical model that suggests that the sensitivity of this sensing system is regulated by changes in the

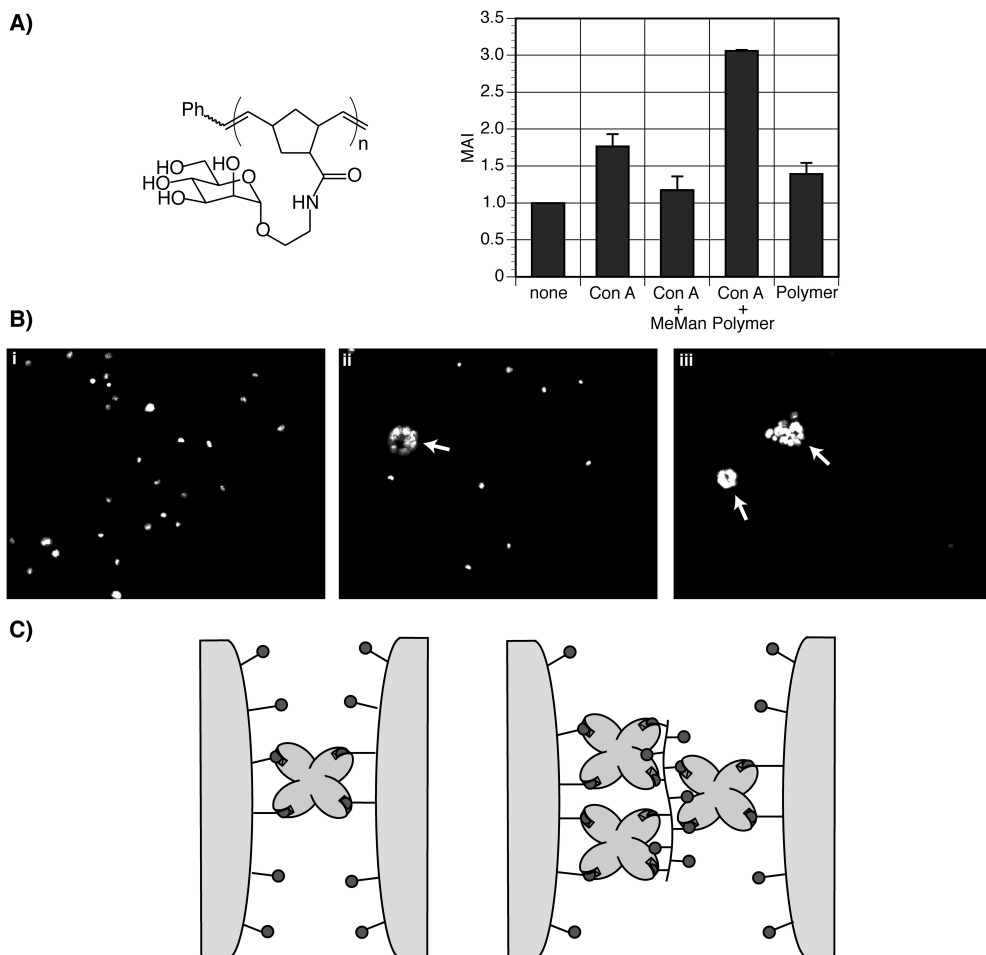
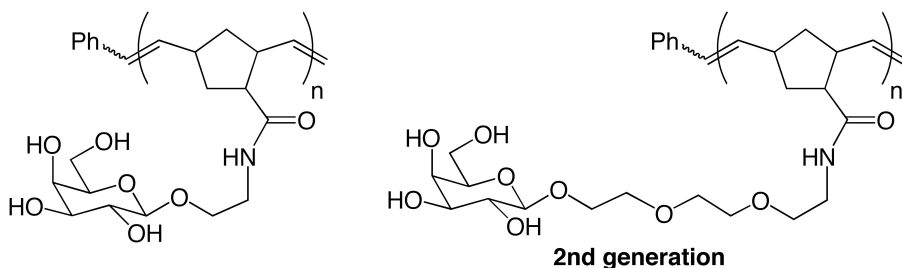


Fig. 3.6-26. Treatment of Con A with mannose-substituted polymers under the appropriate conditions leads to the formation of soluble polymer/Con A clusters. (A) The resulting clusters efficiently mediate cellular aggregation as measured by the macro-molecular aggregation index (MAI) [139]. This degree of aggregation required both polymer and Con A and could be reversed by treatment with a competing ligand such as, α -methyl mannopyranoside. (B) Visual

representation of increased cellular aggregation by polymer/Con A clusters: (i) untreated cells, (ii) Con A-treated cells, (iii) cells treated with soluble Con A/polymer clusters. (C) A model for the improved aggregation of cells by the Con A/polymer complexes. Non-covalent attachment of multiple Con A tetramers to the polymer backbone results in an array of Con A-binding sites, which in turn improve the avidity of Con A for cell surface lectins.

lateral clustering of these bacterial chemoreceptors within the plasma membrane has been proposed [147]. To test this hypothesis, Kiessling and coworkers used ROMP to generate polymers that could be used to probe the role of chemoreceptor clustering.

Kiessling and coworkers synthesized a series of galactose-substituted polymers of different lengths using monomer-to-catalyst ratios of 10:1, 25:1, and 50:1 using emulsion polymerization conditions [148, 149]. Because galactose is an attractant, the multivalent ligands were designed to cluster the galactose-sensing chemoreceptors. Based on molecular modeling studies, the shorter oligomer ($M:I = 10:1$) should be incapable of binding two chemoreceptors simultaneously. The longer polymers, however, were designed to be capable of clustering multiple receptors. This series of ligands, therefore, could be used to investigate whether receptor clustering is involved in the process of chemotaxis. The ability of the galactose-substituted polymers to act as chemoattractants was assessed via standard bacterial behavioral assays (Figure 3.6-27). As predicted, the shortest polymer ($M:I = 10:1$)



Compound	Saccharide Concentration for Maximum Chemotaxis (mM)	Potency
Galactose	1	1
Monomer	1	1
10mer	1	1
2nd Generation 10mer	0.25	4
25mer	0.25	4
2nd Generation 25mer	0.1	10
50mer	0.1	10

Fig. 3.6-27. Galactose-substituted polymers generated by ROMP promote bacterial chemotaxis. Their activities depend on their degree of polymerization (DP). Polymers with larger DP values are more potent attractants. The concentration of maximal chemotaxis was

determined by using capillary accumulation assays. Chemotactic activity also could be quantified using motion analysis. For examples of the videos, see http://www.chem.wisc.edu/~kiessling/bact_vid [149].

exhibited a potency similar to that of monovalent galactose. However, those polymers synthesized using higher M:I ratios (25:1 and 50:1) were 5 times and 10 times more potent than the monomer at inducing a chemotactic response. These results imply that receptor clustering is involved in the regulation of bacterial chemotaxis and that materials that stabilize chemoreceptor clusters influence the behavior of the bacteria. Although this relationship also suggests that the degree of signal amplification is related to the ability of the polymeric attractant to cluster chemoreceptors, it is difficult to dissect local concentration effects from effects due to clustering.

Gestwicki et al. examined the ability of their polymers to cluster chemoreceptors in *E. coli* by fluorescence microscopy. Wild-type *E. coli* localize their chemoreceptors to their poles (Figure 3.6-28A); however, inactivation of a key structural protein, *cheW*, leads to the random distribution of the chemoreceptors on the bacterial surface (Figure 3.6-28B) [150]. Treatment of *cheW* mutants with a galactose-

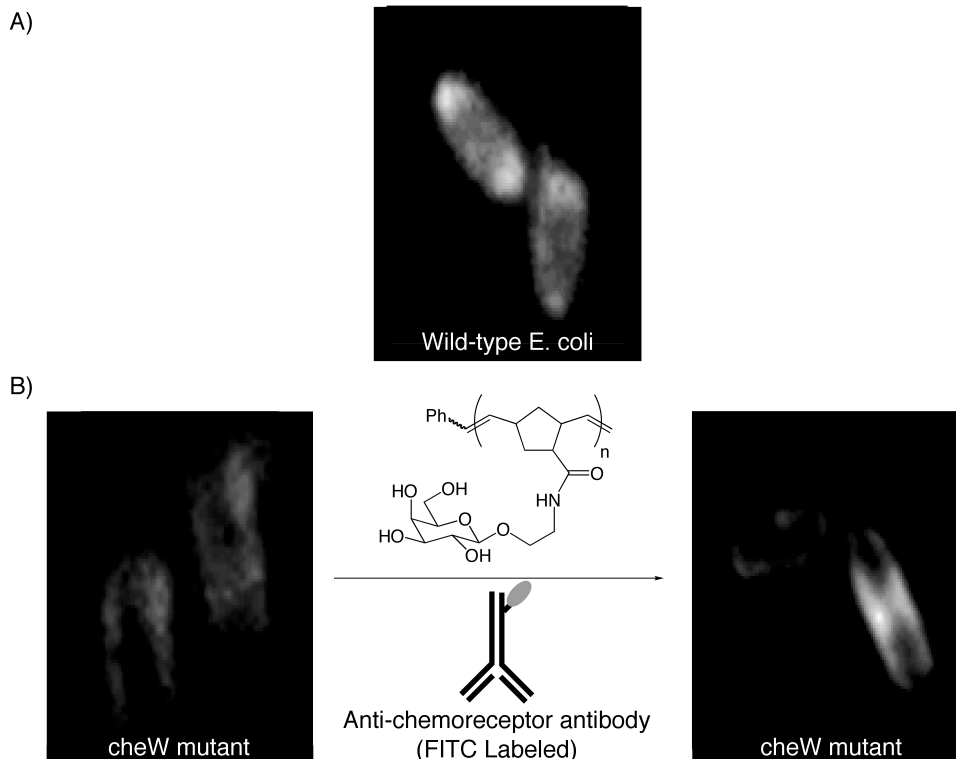


Fig. 3.6-28. Galactose-substituted polymers generated by ROMP promote clustering of chemoreceptors. (A) Chemoreceptors in wild-type *E. coli* are localized at the bacterial poles. Chemoreceptors were visualized using an anti-receptor antibody labeled with fluorescein

isothiocyanate (FITC), as represented by the schematic illustration [148]. (B) In a *cheW* mutant, the receptors distribute around the cell (left). The addition of polymers to the *cheW* mutant results in chemoreceptor clustering (right).

substituted polymer ($M:I = 25:1$, $DP = 38$) results in clustering of the chemoreceptors.

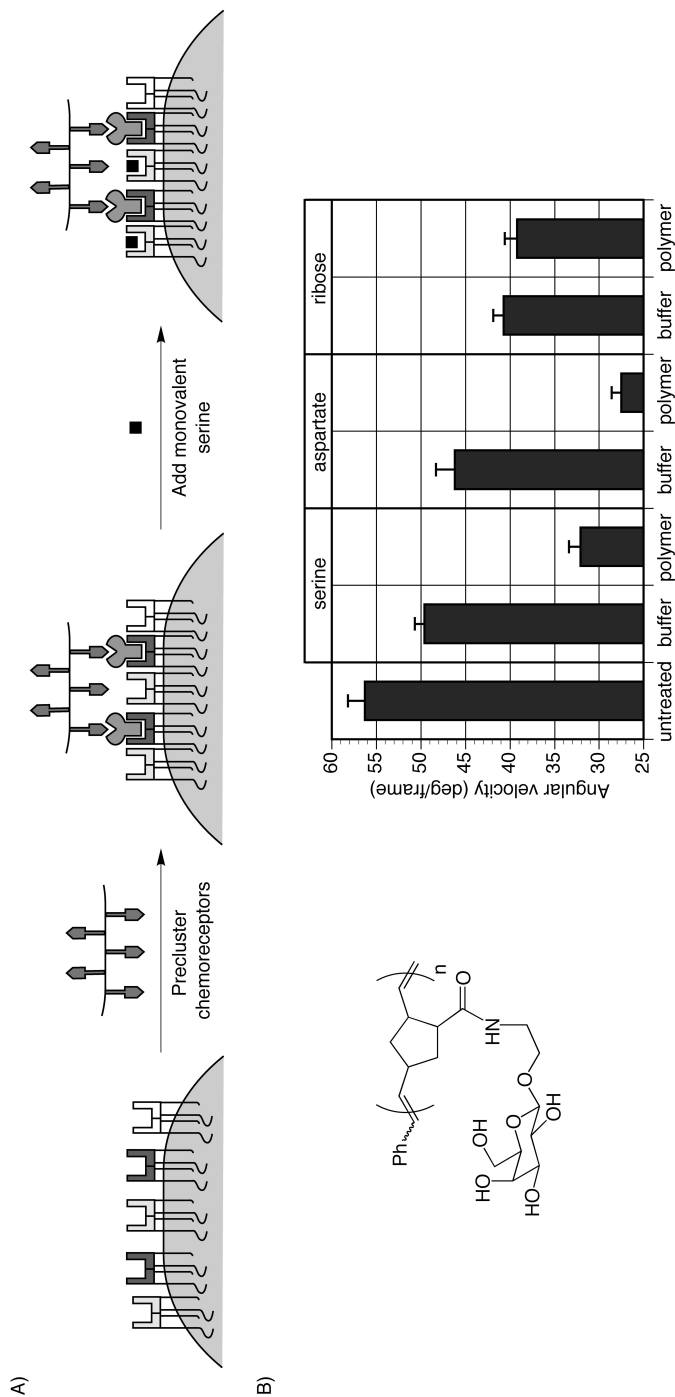
Additional experiments with galactose-substituted ligands generated by ROMP suggested that the polymers cluster not only the galactose-sensing receptor Trg but also the other chemoreceptors. This result indicates that the galactose-substituted polymers may also influence bacterial chemotaxis through inter-receptor communication. To test this hypothesis, *E. coli* were treated with either a galactose-substituted monomer or a galactose-substituted polymer ($DP = 38$), followed by addition of another chemoattractant (e.g., monovalent serine or aspartic acid). By pretreating the bacteria with the polymer, the authors reasoned that the clustering of the chemoreceptors would be enhanced. By adding another attractant, the signal strength arising from the clustered receptors could be determined. They found that pretreatment with the galactose-substituted polymer resulted in amplification of the chemotactic response to serine or aspartate (Figure 3.6-29) [109]. These studies indicate that signals are amplified when receptors are clustered and that one receptor (e.g., galactose-sensing) can influence the activity of another receptor (e.g., serine-sensing). Thus, inter-receptor communication plays an important role in modulating *E. coli*'s sensitivity to chemoattractants. In addition, the results demonstrate that the chemoreceptors act together to sense and integrate attractant signals. These experiments highlight the utility of ROMP-derived materials in the exploration of fundamental questions in cell biology.

3.6.4

Conclusions

The application of ROMP to the construction of novel biologically active materials is a promising and productive research area. The living nature of this polymerization coupled with the functional group tolerance of the metal-carbene initiators has allowed for the synthesis of highly functionalized materials. These include compounds that display carbohydrate epitopes, peptide sequences, nucleic acid bases, and antibiotics. Advances in methods for the conjugation of biological epitopes to monomers and polymers are providing access to novel biomaterials. Methods to selectively end label polymers can be used to install reporter groups or immobilize polymers. Further advances in metal-carbene catalyst design will expand the range and properties of biologically active materials that can be generated.

Materials generated by ROMP have been used in the investigation of a diverse range of biological systems. In particular, ROMP has been used to synthesize potent inhibitors of receptor-ligand interactions, novel antibiotics, and mechanistic probes of multivalent interactions. With regard to the latter, ligands generated by ROMP have been applied to elucidating the consequences of receptor clustering in bacterial chemotaxis and the inflammatory response. Thus, by coupling advances in polymer chemistry with knowledge of the important questions in biology, innovative materials and important new insights will emerge. ROMP will play a prominent role in these endeavors.



receptors may afford an enhanced chemotactic response. (B) Pretreatment of bacteria with multivalent ligands that display galactose (DP = 38) increases the chemotactic potency of monovalent serine and aspartic acid as measured by motion analysis [109].

Fig. 3.6-29. Polymeric ligands stabilize inter-chemoreceptor contacts. (A) Binding of a galactose-substituted polymer promotes clustering of the chemoreceptors including those that are unoccupied. Upon addition of a second, monovalent attractant (back square representing serine), the clustered chemo-

References

- 1 M. MAMMEN, S.-K. CHOI, G. M. WHITESIDES, *Angew. Chem. Int. Ed.* **1998**, 37, 2754–2794.
- 2 C. R. BERTOZZI, L. L. KIESSLING, *Science* **2001**, 291, 2357–2364.
- 3 L. L. KIESSLING, J. E. GESTWICKI, L. E. STRONG, *Curr. Opin. Chem. Biol.* **2000**, 4, 696–703.
- 4 M. J. SOTH, J. S. NOWICK, *Curr. Opin. Chem. Biol.* **1997**, 1, 120–129.
- 5 K. KIRSCHENBAUM, R. N. ZUCKERMAN, K. A. DILL, *Curr. Opin. Struct. Biol.* **1999**, 9, 530–535.
- 6 L. L. KIESSLING, L. E. STRONG, J. E. GESTWICKI, *Annu. Rep. Med. Chem.* **2000**, 35, 321–330.
- 7 N. V. BOVIN, *Glycoconjugate J.* **1998**, 15, 431–446.
- 8 T. K. LINDHORST, *Top. Curr. Chem.* **2002**, 218, 201–235.
- 9 L. L. KIESSLING, L. E. STRONG, *Top. Organomet. Chem.* **1998**, 1, 199–231.
- 10 B. T. HOUSEMAN, M. MRKSICH, *Top. Curr. Chem.* **2002**, 218, 1–44.
- 11 H. M. DINTZIS, R. Z. DINTZIS, B. VOGELSTEIN, *Proc. Natl. Acad. Sci. U. S. A.* **1976**, 73, 3671–3675.
- 12 J. KLEIN, A. H. BEGLI, *Makromol. Chem.* **1989**, 190, 2527–2534.
- 13 H. KAMITAKAHARA, T. SUZUKI, N. NISHIGORI, Y. SUZUKI, O. KANIE, C. H. WONG, *Angew. Chem. Int. Ed.* **1998**, 37, 1524–1528.
- 14 P. H. WEIGEL, R. L. SCHNAAR, M. S. KUHLENSCHMIDT, M. S. SCHMELL, R. T. LEE, Y. C. LEE, S. ROSEMAN, *J. Biol. Chem.* **1979**, 254, 10830–10838.
- 15 A. SPALTENSTEIN, G. M. WHITESIDES, *J. Am. Chem. Soc.* **1991**, 113, 686–687.
- 16 J. Q. WANG, X. CHEN, W. ZHANG, S. ZACHAREK, Y. S. CHEN, P. G. WANG, *J. Am. Chem. Soc.* **1999**, 121, 8174–8181.
- 17 R. ROY, W. K. C. PARK, O. P. SRIVASTAVA, C. FOXALL, *Bioorg. Med. Chem. Lett.* **1996**, 6, 1399–1402.
- 18 H. MIYAUCHI, M. TANAKA, H. KOIKE, N. KAWAMURA, M. HAYASHI, *Bioorg. Med. Chem. Lett.* **1997**, 7, 985–988.
- 19 J. D. REUTER, A. MYC, M. M. HAYES, Z. H. GAN, R. ROY, D. J. QIN, R. YIN, L. T. PIEHLER, R. ESFAND, D. A. TOMALIA, J. R. BAKER, *Bioconjugate Chem.* **1999**, 10, 271–278.
- 20 K. YAMADA, M. MINODA, T. MIYAMOTO, *Macromolecules* **1999**, 32, 3553–3558.
- 21 K. YAMADA, M. MINODA, T. FUKUDA, T. MIYAMOTO, *J. Polym. Sci. Pol. Chem.* **2001**, 39, 459–467.
- 22 T. J. DEMING, *J. Polym. Sci. Pol. Chem.* **2000**, 38, 3011–3018.
- 23 J. J. CHENG, T. J. DEMING, *Macromolecules* **2001**, 34, 5169–5174.
- 24 X. L. SUN, D. GRANDE, S. BASKARAN, S. R. HANSON, E. L. CHAIKOF, *Biomacromolecules* **2002**, 3, 1065–1070.
- 25 K. OHNO, Y. IZU, S. YAMAMOTO, T. MIYAMOTO, T. FUKUDA, *Macromol. Chem. Phys.* **1999**, 200, 1619–1625.
- 26 Z. C. LI, Y. Z. LIANG, G. Q. CHEN, F. M. LI, *Macromol. Rapid Commun.* **2000**, 21, 375–380.
- 27 K. MATYJASZEWSKI, J. H. XIA, *Chem. Rev.* **2001**, 101, 2921–2990.
- 28 M. KAMIGAITO, T. ANDO, M. SAWAMOTO, *Chem. Rev.* **2001**, 101, 3689–3745.
- 29 T. M. TRNKA, R. H. GRUBBS, *Acc. Chem. Res.* **2001**, 34, 18–29.
- 30 M. R. BUCHMEISER, *Chem. Rev.* **2000**, 100, 1565–1604.
- 31 J.-L. HÉRISSON, Y. CHAUVIN, *Makromol. Chem.* **1971**, 141, 161–167.
- 32 P. SCHWAB, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1996**, 118, 100–110.
- 33 R. R. SCHROCK, *Tetrahedron* **1999**, 55, 8141–8153.
- 34 D. ALBAGLI, G. C. BAZAN, R. R. SCHROCK, M. S. WRIGHTON, *J. Phys. Chem.* **1993**, 97, 10211–10216.
- 35 D. ALBAGLI, G. C. BAZAN, R. R. SCHROCK, M. S. WRIGHTON, *J. Am. Chem. Soc.* **1993**, 115, 7328–7334.
- 36 R. M. OWEN, J. E. GESTWICKI, T. YOUNG, L. L. KIESSLING, *Org. Lett.* **2002**, 4, 2293–2296.
- 37 E. J. GORDON, J. E. GESTWICKI, L. E. STRONG, L. L. KIESSLING, *Chem. Biol.* **2000**, 7, 9–16.
- 38 G. NOMURA, S. TAKAHASHI, Y. IMANISHI, *Macromolecules* **2001**, 34, 4712–4723.

- 39 S. K. ARMSTRONG, *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.
- 40 C. W. BIELAWSKI, R. H. GRUBBS, *Macromolecules* **2001**, *34*, 8838–8840.
- 41 D. A. ROBSON, V. C. GIBSON, R. G. DAVIES, M. NORTH, *Macromolecules* **1999**, *32*, 6371–6373.
- 42 T.-L. CHOI, R. H. GRUBBS, *Angew. Chem. Int. Ed.* **2003**, *42*, 1743–1746.
- 43 B. M. NOVAK, R. H. GRUBBS, *J. Am. Chem. Soc.* **1988**, *110*, 960–961.
- 44 K. H. MORTELL, M. GINGRAS, L. L. KIESSLING, *J. Am. Chem. Soc.* **1994**, *116*, 12053–12054.
- 45 M. C. SCHUSTER, K. H. MORTELL, A. D. HEGEMAN, E. L. KIESSLING, *J. Mol. Catal. A-Chem.* **1997**, *116*, 209–216.
- 46 C. FRASER, R. H. GRUBBS, *Macromolecules* **1995**, *28*, 7248–7255.
- 47 S. T. NGUYEN, R. H. GRUBBS, J. W. ZILLER, *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.
- 48 K. NOMURA, R. R. SCHROCK, *Macromolecules* **1996**, *29*, 540–545.
- 49 D. M. LYNN, S. KANAOKA, R. H. GRUBBS, *J. Am. Chem. Soc.* **1996**, *118*, 784–790.
- 50 N. L. POHL, L. L. KIESSLING, *Synthesis* **1999**, 1515–1519.
- 51 E. J. GORDON, L. E. STRONG, L. L. KIESSLING, *Bioorg. Med. Chem.* **1998**, *6*, 1–7.
- 52 D. D. MANNING, X. HU, P. BECK, L. L. KIESSLING, *J. Am. Chem. Soc.* **1997**, *119*, 3161–3162.
- 53 D. D. MANNING, L. E. STRONG, X. HU, P. J. BECK, L. L. KIESSLING, *Tetrahedron* **1997**, *53*, 11937–11952.
- 54 E. J. GORDON, W. J. SANDERS, L. L. KIESSLING, *Nature* **1998**, *392*, 30–31.
- 55 W. J. SANDERS, E. J. GORDON, O. DWIR, P. J. BECK, R. ALON, L. L. KIESSLING, *J. Biol. Chem.* **1999**, *274*, 5271–5278.
- 56 M. KANAI, K. H. MORTELL, L. L. KIESSLING, *J. Am. Chem. Soc.* **1997**, *119*, 9931–9932.
- 57 M. KANAI AND L. L. KIESSLING, unpublished results.
- 58 S. MEIER, H. REISINGER, R. HAAG, S. MECKING, R. MÜLHAUPT, F. STELZER, *Chem. Commun.* **2001**, 855–856.
- 59 S. C. G. BIAGINI, M. P. COLES, V. C. GIBSON, M. R. GILES, E. L. MARSHALL, M. NORTH, *Polymer* **1998**, *39*, 1007–1014.
- 60 M. P. COLES, V. C. GIBSON, L. MAZZARIOL, M. NORTH, W. G. TEASDALE, C. M. WILLIAMS, D. ZAMUNER, *J. Chem. Soc.-Chem. Commun.* **1999**, 2505–2506.
- 61 S. C. G. BIAGINI, R. G. DAVIES, V. C. GIBSON, M. R. GILES, E. L. MARSHALL, M. NORTH, *Polymer* **2001**, *42*, 6669–6671.
- 62 J. WANNER, A. M. HARNED, D. A. PROBST, K. W. C. POON, T. A. KLEIN, K. A. SNELGROVE, P. R. HANSON, *Tetrahedron Lett.* **2002**, *43*, 917–921.
- 63 M. SCHOLL, S. DING, C. W. LEE, R. H. GRUBBS, *Org. Lett.* **1999**, *1*, 953–956.
- 64 H. D. MAYNARD, S. Y. OKADA, R. H. GRUBBS, *Macromolecules* **2000**, *33*, 6239–6248.
- 65 H. D. MAYNARD, S. Y. OKADA, R. H. GRUBBS, *J. Am. Chem. Soc.* **2001**, *123*, 1275–1279.
- 66 J. MICKLEFIELD, *Curr. Med. Chem.* **2001**, *8*, 1157–1179.
- 67 M. J. HAN, J. Y. CHANG, *Adv. Polym. Sci.* **2000**, *153*, 1–36.
- 68 V. C. GIBSON, E. L. MARSHALL, M. NORTH, D. A. ROBSON, P. J. WILLIAMS, *Chem. Commun.* **1997**, 1095–1096.
- 69 R. G. DAVIES, V. C. GIBSON, M. B. HURSTHOUSE, M. E. LIGHT, E. L. MARSHALL, M. NORTH, D. A. ROBSON, I. THOMPSON, A. J. P. WHITE, D. J. WILLIAMS, P. J. WILLIAMS, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3365–3381.
- 70 T. Y. LEE, Y. B. SHIM, *Anal. Chem.* **2001**, *73*, 5629–5632.
- 71 H. KORRI-YOUSOUFI, A. YASSAR, *Biomacromolecules* **2001**, *2*, 58–64.
- 72 N. LASSALLE, A. ROGET, T. LIVACHE, P. MAILLEY, E. VIEIL, *Talanta* **2001**, *55*, 993–1004.
- 73 K. J. WATSON, S. J. PARK, J. H. IM, S. T. NGUYEN, C. A. MIRKIN, *J. Am. Chem. Soc.* **2001**, *123*, 5592–5593.
- 74 A. GODWIN, K. BOLINA, M. CLOCHARD, E. DINAND, S. RANKIN, S. SIMIC, S. BROCCINI, *J. Pharm. Pharmacol.* **2001**, *53*, 1175–1184.
- 75 S. C. G. BIAGINI, V. C. GIBSON, M. R. GILES, E. L. MARSHALL, M. NORTH, *Chem. Commun.* **1997**, 1097–1098.
- 76 K. J. WATSON, D. R. ANDERSON, S. T.

- NGUYEN, *Macromolecules* **2001**, *34*, 3507–3509.
- 77 H. ARIMOTO, K. NISHIMURA, T. KINUMI, I. HAYAKAWA, D. UEMURA, *Chem. Commun.* **1999**, 1361–1362.
- 78 G. B. SIGAL, M. MAMMEN, G. DAHMANN, G. M. WHITESIDES, *J. Am. Chem. Soc.* **1996**, *118*, 3789–3800.
- 79 G. THOMA, J. L. MAGNANI, R. OHRLEIN, B. ERNST, F. SCHWARZENBACH, R. O. DUTHALER, *J. Am. Chem. Soc.* **1997**, *119*, 7414–7415.
- 80 T. ARNAULD, A. G. M. BARRETT, S. M. CRAMP, R. S. ROBERTS, F. J. ZECRI, *Org. Lett.* **2000**, *2*, 2663–2666.
- 81 A. G. M. BARRETT, B. T. HOPKINS, J. KOBBERLING, *Chem. Rev.* **2002**, *102*, 3301–3323.
- 82 L. E. STRONG, L. L. KIESSLING, *J. Am. Chem. Soc.* **1999**, *121*, 6193–6196.
- 83 A. GODWIN, M. HARTENSTEIN, A. H. E. MULLER, S. BROCCINI, *Angew. Chem. Int. Ed.* **2001**, *40*, 594–597.
- 84 M. MOUREZ, R. S. KANE, J. MOGRIDGE, S. METALLO, P. DESCHATELETS, B. R. SELLMAN, G. M. WHITESIDES, R. J. COLLIER, *Nature Biotechnol.* **2001**, *19*, 958–961.
- 85 M. TICHA, J. KOCOUREK, *Carbohydr. Res.* **1991**, *213*, 339–343.
- 86 J. E. GESTWICKI, C. W. CAIRO, D. A. MANN, R. M. OWEN, L. L. KIESSLING, *Anal. Biochem.* **2002**, *305*, 149–155.
- 87 E. J. GORDON, Ph. D. Dissertation, University of Wisconsin, Madison, WI, 1998.
- 88 T. FEIZI, *Immunol. Rev.* **2000**, *173*, 79–88.
- 89 R. ROY, *Curr. Opin. Struc. Biol.* **1996**, *6*, 692–702.
- 90 J. C. SACCHETTINI, L. G. BAUM, C. F. BREWER, *Biochemistry* **2001**, *40*, 3009–3015.
- 91 Y. C. LEE, R. T. LEE, *Acc. Chem. Res.* **1995**, *28*, 321–327.
- 92 K. H. MORTELL, R. V. WEATHERMAN, L. L. KIESSLING, *J. Am. Chem. Soc.* **1996**, *118*, 2297–2298.
- 93 J. J. LUNDQUIST, E. J. TOONE, *Chem. Rev.* **2002**, *102*, 555–578.
- 94 P. I. KITOV, J. M. SADOWSKA, G. MULVEY, G. D. ARMSTRONG, H. LING, N. S. PANNU, R. J. READ, D. R. BUNDLE, *Nature* **2000**, *403*, 669–672.
- 95 E. K. FAN, Z. S. ZHANG, W. E. MINKE, Z. HOU, C. VERLINDE, W. G. J. HOL, *J. Am. Chem. Soc.* **2000**, *122*, 2663–2664.
- 96 J. B. CORBELL, J. J. LUNDQUIST, E. J. TOONE, *Tetrahedron: Asymmetry* **2000**, *11*, 95–111.
- 97 I. VRASIDAS, N. J. DE MOL, R. M. J. LISKAMP, R. J. PIETERS, *Eur. J. Org. Chem.* **2001**, 4685–4692.
- 98 G. D. GLICK, P. L. TOOGOOD, D. C. WILEY, J. J. SKEHEL, J. R. KNOWLES, *J. Biol. Chem.* **1991**, *266*, 23660–23669.
- 99 S. ANDRE, P. J. C. ORTEGA, M. A. PEREZ, R. ROY, H. J. GABIUS, *Glycobiology* **1999**, *9*, 1253–1261.
- 100 J. E. GESTWICKI, C. W. CAIRO, L. E. STRONG, K. A. OETJEN, L. L. KIESSLING, *J. Am. Chem. Soc.* **2002**.
- 101 C. W. CAIRO, J. E. GESTWICKI, M. KANAI, L. L. KIESSLING, *J. Am. Chem. Soc.* **2002**, *124*, 1615–1619.
- 102 D. A. MANN, M. KANAI, D. J. MALY, L. L. KIESSLING, *J. Am. Chem. Soc.* **1998**, *120*, 10575–10582.
- 103 H. BITTIGER, H. P. SCHNEBLI, Eds., *Concanavalin A as a Tool*, John Wiley & Sons: Ltd., London, 1976.
- 104 J. E. GESTWICKI, L. E. STRONG, L. L. KIESSLING, *Angew. Chem. Int. Ed.* **2000**, *39*, 4567–4570.
- 105 J. R. COCHRAN, T. O. CAMERON, L. J. STERN, *Immunity* **2000**, *12*, 241–250.
- 106 E. K. GRIFFITHS, C. KRAWCZYK, Y. Y. KONG, M. RAAB, S. J. HYDUK, D. BOUCHARD, V. S. CHAN, I. KOZIERADZKI, A. J. OLIVEIRA-DOS-SANTOS, A. WAKEHAM, P. S. OHASHI, M. I. CYBULSKY, C. E. RUDD, J. M. PENNINGER, *Science* **2001**, *293*, 2260–2263.
- 107 G. MAHESHWARI, G. BROWN, D. A. LAUFFENBURGER, A. WELLS, L. G. GRIFFITH, *J. Cell Sci.* **2000**, *113*, 1677–1686.
- 108 A. VIOLA, S. SCHROEDER, Y. SAKAKIBARA, A. LANZAVECCHIA, *Science* **1999**, *283*, 680–682.
- 109 J. E. GESTWICKI, L. L. KIESSLING, *Nature* **2002**, *415*, 81–84.
- 110 K. D. PATEL, S. L. CUVELIER, S. WIEHLER, *Semin. Immunol.* **2002**, *14*, 73–81.
- 111 R. P. McEVER, *Curr. Opin. Cell Biol.* **2002**, *14*, 581–586.

- 112 R. E. BRUEHL, T. A. SPRINGER, D. F. BAINTON, *J. Histochem. Cytochem.* **1996**, 44, 835–844.
- 113 A. VARKI, *J. Clin. Invest.* **1997**, 99, 158–162.
- 114 S. D. ROSEN, *Am. J. Pathol.* **1999**, 155, 1013–1020.
- 115 J. YANG, B. C. FURIE, B. FURIE, *Thromb. Haemostasis* **1999**, 81, 1–7.
- 116 M. S. MULLIGAN, R. L. WARNER, J. B. LOWE, P. L. SMITH, Y. SUZUKI, M. MIYASAKA, S. YAMAGUCHI, Y. OHTA, Y. TSUKADA, M. KISO, A. HASEGAWA, P. A. WARD, *Int Immunol* **1998**, 10, 569–575.
- 117 Y. SUZUKI, Y. TODA, T. TAMATANI, T. WATANABE, T. SUZUKI, T. NAKAO, K. MURASE, M. KISO, A. HASEGAWA, K. TADANOARITOMI, I. ISHIZUKA, M. MIYASAKA, *Biochem. Biophys. Res. Commun.* **1993**, 190, 426–434.
- 118 E. E. SIMANEK, G. J. MCGARVEY, J. A. JABLONOWSKI, C. H. WONG, *Chem. Rev.* **1998**, 98, 833–862.
- 119 T. M. JUNG, M. O. DAILEY, *J. Immunol.* **1990**, 144, 3130–3136.
- 120 T. K. KISHIMOTO, M. A. JUTILA, E. L. BERG, E. C. BUTCHER, *Science* **1989**, 245, 1238–1241.
- 121 E. S. HARRIS, T. M. MCINTYRE, S. M. PRESCOTT, G. A. ZIMMERMAN, *J. Biol. Chem.* **2000**, 275, 23409–23412.
- 122 E. H. J. DANEN, K. M. YAMADA, *J. Cell Physiol.* **2001**, 189, 1–13.
- 123 C. K. MIRANTI, J. S. BRUGGE, *Nature Cell. Biol.* **2002**, 4, E83–E90.
- 124 A. VAN DER FLIER, A. SONNENBERG, *Cell Tissue Res.* **2001**, 305, 285–298.
- 125 S. A. MOUSA, *Curr. Opin. Chem. Biol.* **2002**, 6, 534–541.
- 126 G. P. CURLEY, H. BLUM, M. J. HUMPHRIES, *Cell. Mol. Life Sci.* **1999**, 56, 427–441.
- 127 S. AOTA, M. NOMIZU, K. M. YAMADA, *J. Biol. Chem.* **1994**, 269, 24756–24761.
- 128 B. H. NORMARK, S. NORMARK, *J. Intern. Med.* **2002**, 252, 91–106.
- 129 M. LIPSITCH, *Trends Microbiol.* **2001**, 9, 438–444.
- 130 C. WALSH, *Nature* **2000**, 406, 775–781.
- 131 J. M. HAMILTON-MILLER, *Infection* **2002**, 30, 118–124.
- 132 H. PEARSON, *Nature* **2002**, 418, 469–469.
- 133 D. H. WILLIAMS, B. BARDSLEY, *Angew. Chem. Int. Edit.* **1999**, 38, 1173–1193.
- 134 R. LECLERCQ, P. COURVALIN, *Clin. Infect. Dis.* **1997**, 24, 545–556.
- 135 C. T. WALSH, S. L. FISHER, I. S. PARK, M. PRAHALAD, Z. WU, *Chem. Biol.* **1996**, 3, 21–28.
- 136 J. H. RAO, J. LAHIRI, L. ISAACS, R. M. WEIS, G. M. WHITESIDES, *Science* **1998**, 280, 708–711.
- 137 U. N. SUNDRAM, J. H. GRIFFIN, T. I. NICAS, *J. Am. Chem. Soc.* **1996**, 118, 13107–13108.
- 138 H. ARIMOTO, T. OISHI, M. NISHIJIMA, T. KINUMI, *Tetrahedron Lett.* **2001**, 42, 3347–3350.
- 139 J. E. GESTWICKI, L. E. STRONG, C. W. CAIRO, F. J. BOEHM, L. L. KIESSLING, *Chem. Biol.* **2002**, 9, 163–169.
- 140 R. P. TAYLOR, W. M. SUTHERLAND, E. N. MARTIN, P. J. FERGUSON, M. L. REINAGEL, E. GILBERT, K. LOPEZ, N. L. INCARDONA, H. D. OCHS, *J. Immunol.* **1997**, 158, 842–850.
- 141 M. A. LINDORFER, C. S. HAHN, P. L. FOLEY, R. P. TAYLOR, *Immunol. Rev.* **2001**, 183, 10–24.
- 142 J. ADLER, *Annu. Rev. Biochem.* **1975**, 44, 341–356.
- 143 A. BREN, M. EISENBACH, *J. Bacteriol.* **2000**, 182, 6865–6873.
- 144 J. J. FALKE, R. B. BASS, S. L. BUTLER, S. A. CHERVITZ, M. A. DANIELSON, *Annu. Rev. Cell. Dev. Biol.* **1997**, 13, 457–512.
- 145 R. B. BOURRET, A. M. STOCK, *J. Biol. Chem.* **2002**, 277, 9625–9628.
- 146 R. MESIBOV, J. ADLER, *J. Bacteriol.* **1972**, 112, 315–326.
- 147 D. BRAY, M. D. LEVIN, C. J. MORTON-FIRTH, *Nature* **1998**, 393, 85–88.
- 148 J. E. GESTWICKI, L. E. STRONG, L. L. KIESSLING, *Chem. Biol.* **2000**, 7, 583–591.
- 149 J. E. GESTWICKI, L. E. STRONG, S. L. BORCHARDT, C. W. CAIRO, A. M. SCHNOES, L. L. KIESSLING, *Bioorg. Med. Chem.* **2001**, 9, 2387–2393.
- 150 J. R. MADDOCK, L. SHAPIRO, *Science* **1993**, 259, 1717–1723.

3.7

Metathesis Polymerization: A Versatile Tool for the Synthesis of Surface-Functionalized Supports and Monolithic Materials

Michael R. Buchmeiser

3.7.1

Introduction

Surface-modified materials are of enormous importance in many areas of chemistry and materials science. Besides of “daily life” applications such as coatings, paintings, and colored clothing, more sophisticated topics are surface-modified supports for separation science, heterogeneous catalysis, or molecular electronics. As a direct consequence of the development of stable, well-characterized, and well-understood initiators for metathesis polymerization techniques such as ring-opening metathesis polymerization (ROMP), acyclic diene metathesis (ADMET) polymerization, 1-alkyne, and diyne cyclopolymerization, these transition metal-based initiators have been applied to the synthesis of surface-modified or functionalized materials. Only when well-defined systems such as the Schrock (typically of the general formula $\text{Mo}(N\text{-}2,6\text{-R}_2\text{-C}_6\text{H}_3)(\text{CHCMe}_2\text{Ph})(\text{OR}')_2$) ($\text{R} = \text{Me}$, $i\text{-Pr}$, $\text{R}' = \text{tert.-Bu}$, $\text{CMe}(\text{CF}_3)_2$, etc.) or first- and second-generation Grubbs initiators ($\text{Cl}_2\text{Ru}(\text{CHPh})(\text{PR}'')_2$, $\text{Cl}_2\text{Ru}(\text{CHPh})(\text{NHC})(\text{PR}'')_3$, ($\text{R}'' = \text{Ph}$, cyclohexyl, $\text{NHC} = \text{a } N\text{-heterocyclic carbene}$) are used [1] does one create “living” polymerization setups and gain access to a broad variety of polymeric architectures, including block or random copolymers as well as telechelic polymers. In contrast to early transition metal chemistry, these initiators are functionality tolerant. Though the term “functionality” is, at least in its abstract form, certainly applicable to any chemical group, the term “functional group,” in particular in view of a certain application, always refers to more complex architectures. In this chapter, significant achievements in the metathesis polymerization-based synthesis of surface-functionalized supports are summarized.

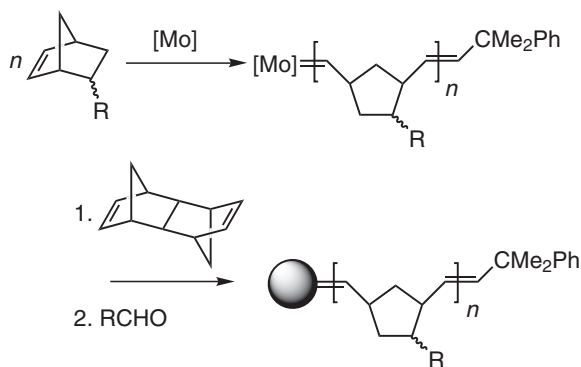
3.7.2

Precipitation Polymerization-Based Techniques

Taking advantage of the capability of the above-mentioned initiators to polymerize functional monomers, a conceptually new ROMP-based approach, which allows

the synthesis of such supports by a convergent synthetic route starting from functional monomers, was developed. In addition to existing metathesis-based polymerization techniques such as ring-opening metathesis polymerization (ROMP), acyclic diene metathesis polymerization, and 1-alkyne polymerization [5], ring-opening metathesis precipitation polymerization was developed as an attractive technique for the synthesis of complex, cross-linked architectures. In a first step, the synthesis of high-capacity anion exchange supports based on poly(norborn-2-ene-5,6-dicarboxylic anhydride) was developed [8]. The synthetic concept was based on a living polymerization of a functional monomer, followed by addition of a cross-linker. The living polymerization system must fulfill the criteria of a class VI living system according to Matyjaszewsky [9] for both the monomer and the cross-linker in order to obtain quantitative conversion and incorporation of the functional monomer into the support. The solvent system was designed in a way that the living, linear polymer chains precipitated during polymerization prior to addition of the cross-linker. Depending on the polarity of the monomer, CH_2Cl_2 or mixtures of CH_2Cl_2 and diethyl ether were found to be appropriate. Upon addition of a cross-linker (e.g., 1,4,4a,5,8,8a-hexahydro-1,4,5,8-*exo-endo*-dimethanonaphthalene, DMN-H6), irregularly shaped polymer beads with a mean diameter of 40–60 μm were prepared (Scheme 3.7-1) [10–18].

At the end of the reaction, the beads can be filtered and used without sieving. Their size was ideal for their convenient removal at the end of any reaction by means of filtration. Because of their favorable initiation properties, only molybdenum-based initiators were used and were removed quantitatively in a Wittig-type reaction by adding an aldehyde (e.g., ferrocene aldehyde) [2] followed by a subsequent washing step with aqueous base. As a consequence of the entire polymerization setup and sequence, the linear polymer chains built from the functional monomer were located at the surface (or at least at the outer shell) of the beads. Degrees of polymerization up to 50 were found to be appropriate for these “tentacles.” Upon addition of polar solvents such as THF or CH_2Cl_2 , the



Scheme 3.7-1. Synthesis of cross-linked polymer beads via ring-opening metathesis precipitation polymerization.

$[\text{Mo}] = \text{Mo}(N\text{-}2,6\text{-}i\text{-Pr}_2\text{-C}_6\text{H}_3)(=\text{CHCMe}_2\text{Ph})(\text{OCMe}(\text{CF}_3)_2)_2$.

beads showed considerable swelling (20–65%), which directly translated into the data for the specific surface area (σ). Thus, BET measurements of the dry material revealed values of $\sigma \leq 30 \text{ m}^2 \text{ g}^{-1}$, whereas inverse size exclusion chromatography (ISEC) [3, 4] in THF indicated specific surface areas of $\leq 90 \text{ m}^2 \text{ g}^{-1}$. Dicarboxylate-based materials prepared by this concept were successfully used as sorbents in solid-phase extraction (SPE) for the extraction of amines, anilines, lutidines, phenols, alcohols, carboxylic acids, aldehydes, ketones, esters, chloroalkanes, *N*-nitrosoamines, and polycyclic aromatic hydrocarbons (PAHs) at the low ppm ($\mu\text{g g}^{-1}$) respectively ppb (ng g^{-1}) level from water [5–7], as well as for the analysis of airborne volatile amines [8]. The broad applicability of this resin type was additionally demonstrated by its use as ion-exchange material in pre-columns coupled to an ESI-MS. This setup allowed the formation of single-ionized oligonucleotides from mixtures with various degrees of ionization, thus lowering the limit of quantification to the pmol level [9]. Another interesting aspect of these resins was the fact that the dicarboxylate ligand did not change its configuration during polymerization. In fact, this ligand can be regarded as a polymer-bound succinic acid with both acid groups in a *cis*-configuration. Taking advantage of the high affinity of lanthanides for succinic acid, this sorbent was successfully used in the offline extraction of lanthanides at the low ppm level from rock digests [10–12]. A summary of the physical properties of these materials is given in Table 3.7-1.

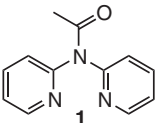
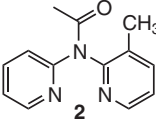
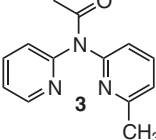
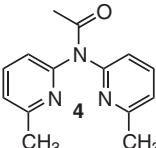
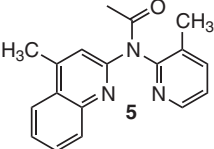
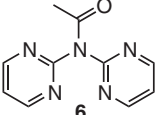
In analogy to carboxylate-functionalized beads, dipyridylamide-based resins were synthesized. In contrast to dipyridylamine, the corresponding amide revealed a high selectivity for both mercury(II) and palladium(II) [13]. This allowed the selective enrichment of these two transition metal ions from aqueous solutions over a concentration range covering several orders of magnitude [14]. In addition, a palladium(II)-loaded resin was successfully used as a heterogeneous Heck, Sonogashira-Hagihara, and amination catalyst [15]. Based on these encouraging results, a variety of different methylpyridyl-, respectively bis(pyrimidyl)-derivatized

Tab. 3.7-1. Poly(norborn-2-ene-5,6-dicarboxylic acid)-, poly(norborn-2-ene-5-dipyridyl carbamide)-, and poly(norborn-2-ene-5-yl(methylpyridyl)-functionalized resins prepared by ring-opening precipitation polymerization [5, 14, 17].

Functional group	Ligand (mmol g ⁻¹)
Succinic acid	7.30
Succinic acid	3.75
Succinic acid	3.13
<i>N,N</i> -dipyrid-2-ylcarbamide	1.0
<i>N,N</i> -dipyrid-2-ylcarbamide	0.6
<i>N</i> -pyrid-2-yl- <i>N</i> -(3-methylpyrid-2-yl)carbamide	0.03
<i>N</i> -pyrid-2-yl- <i>N</i> -(6-methylpyrid-2-yl)carbamide	0.05
<i>N</i> -(6-methylpyrid-2-yl)- <i>N</i> -(4-methylquinolin-2-yl)carbamide	0.05
<i>N,N</i> -bis(pyrimid-2-yl)carbamide	0.2

σ = specific surface, (1) in water, (2) from BET measurements, and (3) calculated from GPC data, average particle size = $40 \pm 10 \mu\text{m}$.

Tab. 3.7-2. Overview of pyrid-2-yl and pyrimid-2-yl ligands **1–6** used for immobilization.

<i>ligand (NBE-R)</i>	<i>coupling reaction</i>
 <p>1</p>	Heck Sonogashira-Hagihara
 <p>2</p>	Heck
 <p>3</p>	Heck
 <p>4</p>	Heck
 <p>5</p>	Heck
 <p>6</p>	Heck Sonogashira-Hagihara Suzuki

supports were prepared from norborn-2-ene-(NBE-)-derived monomers containing ligands **2–6** [15–21]. An overview over these ligands including applications is given in Table 3.7-2.

Typical amounts of the ligands **2–6** immobilized onto the cross-linked support were in the range of 0.03 to 1.0 mmol g⁻¹. Loading of these ligands with Pd(II) results in highly active supports for Pd-mediated C–C coupling reactions. Due to the tentacle-type structure, large amounts of functional groups were again located at the surface. This ensured a fast mass transfer within the interphase [22]. In

addition, the high selectivity of this ligand for Pd(II) [14] and its thermal and oxidative stability make these supports attractive. Furthermore, the synthesis of monomeric, soluble analogues allows mechanistic correlations. Again, both the monomeric and Pd-loaded supports were successfully used in Heck-, Sonogashira-Hagihara-, and Suzuki-type couplings of aryl iodides and bromides, as well as in the *N*-arylation of amines. The heterogeneous systems could be reused and were characterized by high turnover numbers (TONs) up to 22,000. In terms of stoichiometry, the amounts of Pd can be reduced to less than 0.0003 mol%, which illustrates the efficiency of these systems.

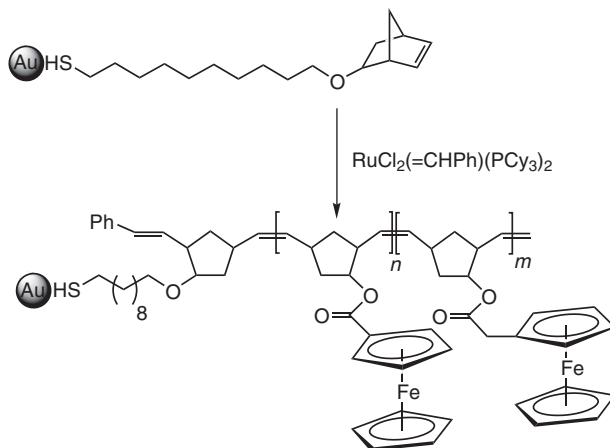
Later, Barrett created the term “ROMPgel” for linear polymers that swell but do not dissolve in certain solvents due to solubility restrictions governed by the nature of the functional monomer used. Such ROMPgels were prepared with a variety of different functional groups, including phosphines [1], allylboronates [23], a polymeric Tosmic reagent [24], naphthalenes and biphenyls [25], alkylphosphonates [26], and anhydrides [27], some in a precipitation polymerization setup similar to the one described by our group (see Chapter 2.10).

3.7.3

Grafting Techniques

The first surface-modification using a “grafting-from” approach was reported by Nguyen et al. They used 1-mercapto-10-(exo-5-norborn-2-enoxy)decane-modified gold nanoparticles for the $\text{Cl}_2\text{Ru}(=\text{CHPh})(\text{PCy}_3)_2$ -initiated grafting of ferrocene-containing norborn-2-enes to produce redox-active polymer nanoparticle hybrid materials (Scheme 3.7-2) [28, 29].

A similar approach was reported by Grubbs and Weiss et al., who used the more rigid tether molecule shown in Figure 3.7-1. *N*-methyl-7-oxanorborn-5-ene-5,6-



Scheme 3.7-2. Synthesis of redox-active polymer nanoparticle hybrid materials.

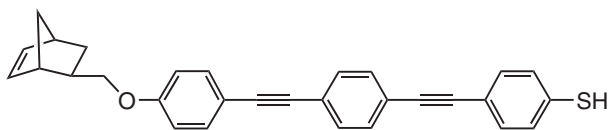


Fig. 3.7-1. Rigid tether molecules used in surface grafting.

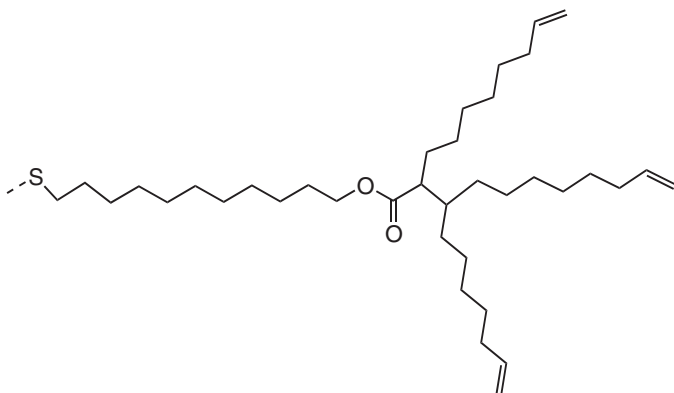


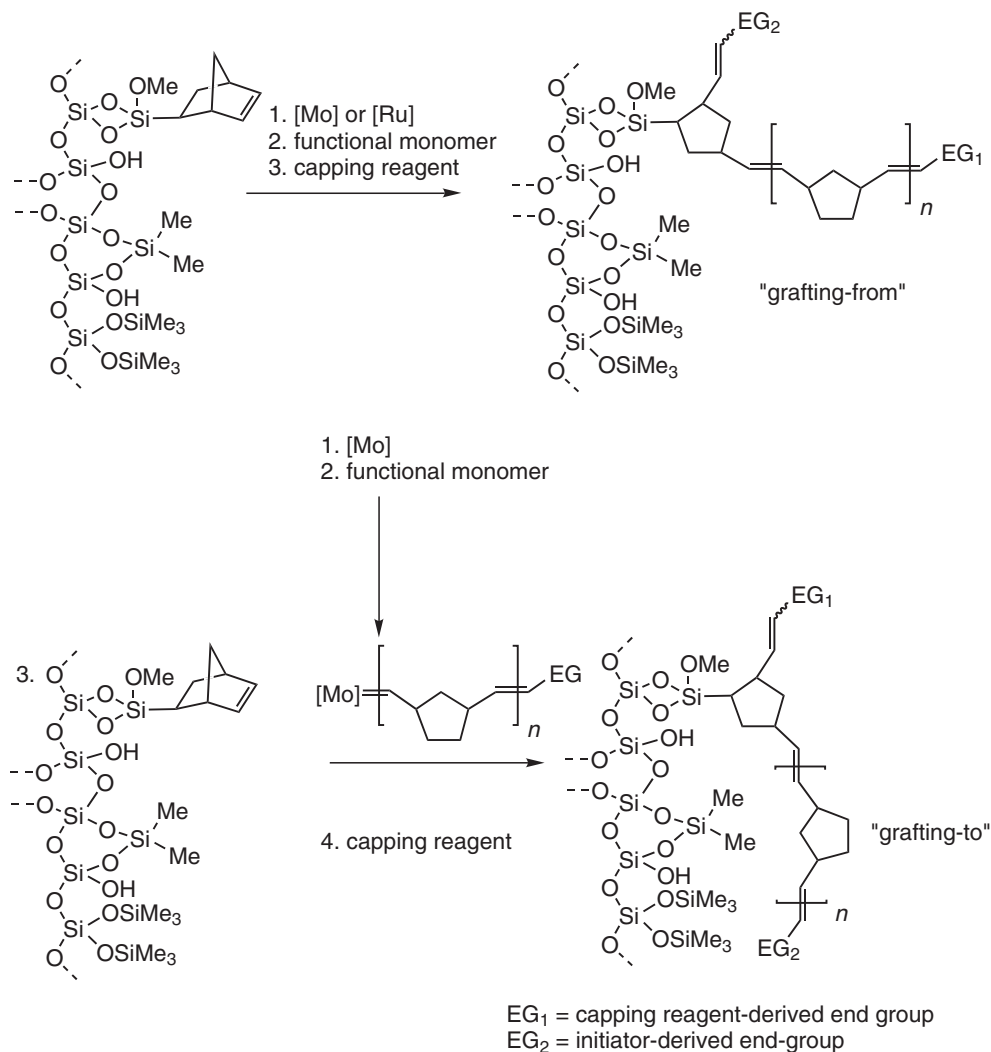
Fig. 3.7-2. Tripodal ligand used in surface grafting.

dicarbimide and 2,3-bis(*tert*-butoxydimethylsilyloxymethylene)-norborn-5-ene were used for the “grafting-from” approach [30].

Shultz, Linderman, and Feldheim described the synthesis of nanometer-sized hollow polymer capsules from polymer-grafted gold particles. A metathesis route employing Grubbs’ first-generation initiator was applied, where the terminal alkene groups of the tripodal Au-immobilized ligand shown in Figure 3.7-2 were cross-linked to form a three-dimensional polymer network. Etching of the gold particles yielded the desired hollow capsules [31].

Due to the considerable swelling that was observed in ring-opening metathesis precipitation polymerization-based polymer supports, we aimed toward entirely pressure-stable, ROMP-based supports. For these purposes, our group developed synthetic protocols for both a grafting-from and a grafting-to approach for the modification of micrometer-sized organic (e.g., PS-DVB) and inorganic (e.g., silica) particles (Scheme 3.7-3) [32–34].

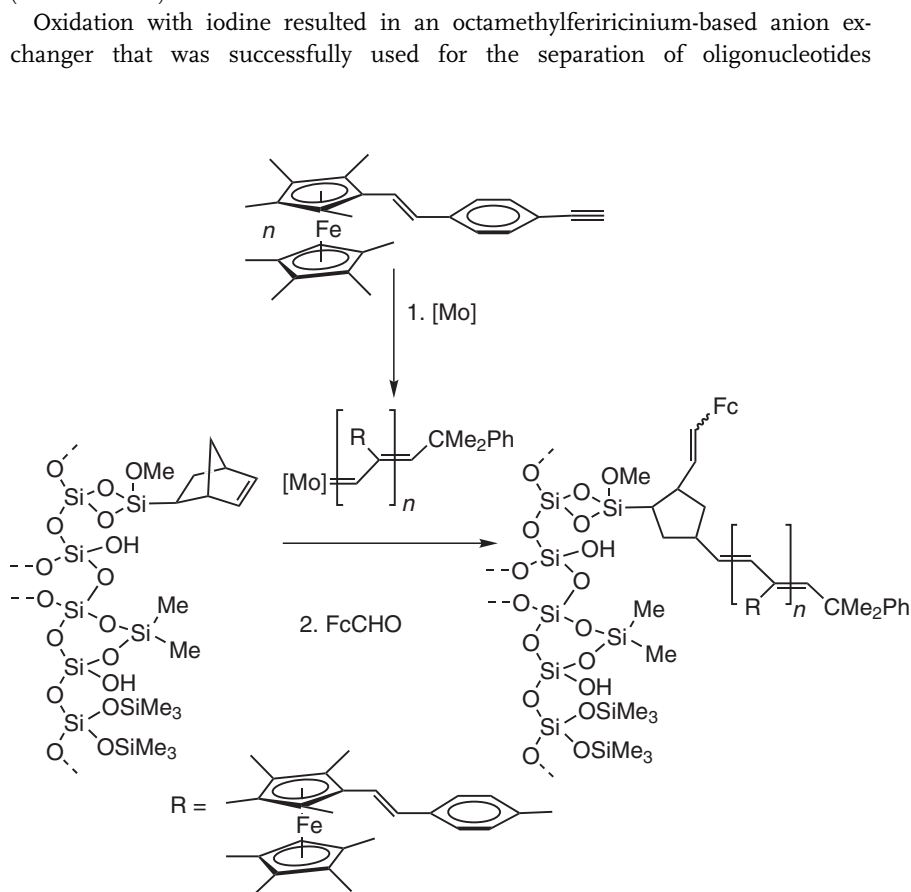
Surface-immobilized norborn-2-ene-5-yl-groups were again used as suitable anchoring groups for the preparation of ROMP-graft copolymers. These were easily introduced in the case of silica materials using trichloro-norborn-2-ene-5-ylsilane or trialkoxy-norborn-2-ene-5-ylsilanes. Subsequent “end capping” with a mixture of chlorotrimethylsilane and dichlorodimethylsilane led to a sufficient derivatization of a major part of the surface silanol groups (approximately 90%). In the case of PS-DVB-based materials, bromomethylation using trioxane, tin tetrabromide, and trimethylbromosilane [35] and, alternatively, conversion of the chloromethyl groups into to the corresponding bromomethyl groups via halogen



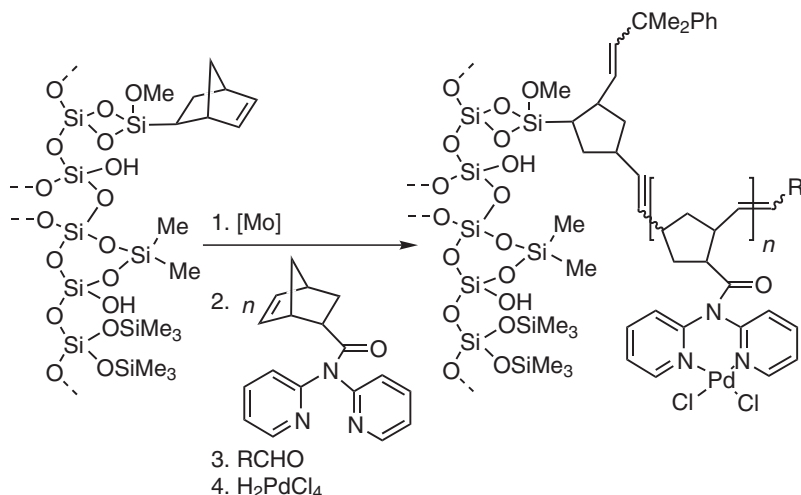
Scheme 3.7-3. General description of the "grafting-from" and "grafting-to" approaches.

exchange [36, 37] was performed. In a final step, the bromomethylated PS-DVB resins were converted into the norborn-2-ene-5-ylmethylethers. For the grafting-to approach, the monomer was transformed into a living polymer via ROMP and subsequently attached to the support by reaction with the surface norborn-2-ene groups. This approach required at least class IV living systems [38] and consequently led to the formation of tentacle-type stationary phases with the linear polymer chains pointing away from the support. Alternatively, the initiator was first reacted with the support to become heterogenized. Monomer was added consecutively and was grafted onto the surface (grafting-from approach). While

first-generation Grubbs-type initiators could be used only for grafting-from experiments, Schrock-type initiators could be used for both methods. In terms of applications, poly-(*N*-(norbornene-5-carboxyl)- β -cyclodextrin ester) as well as poly-(*N*-(norbornene-5-carboxyl)-phenylalanine ethylester) were surface grafted on porous 5 μm silica for applications in chiral HPLC of a large variety of racemic compounds including β -blockers, DNS- or Fmoc-protected amino acids, and planar chiral ferrocene derivatives [39, 40]. In a comparative study, poly(7-oxanorborn-2-ene)-grafted silica supports possessed separation behavior superior to that of the analogous coated separation media [41]. Based on our studies on metallocenyl-alkynes [42–45], poly(ethynylferrocenyl)-based anionic exchangers were prepared following the grafting concept described above [46]. Thus, metathesis polymerization of 4-ethynyl-1-(octamethylferrocenylethenyl)benzene using a Schrock-type catalyst and subsequent grafting of the living polymer onto a NBE-derivatized silica support resulted in the desired octamethylferrocene-grafted stationary phase (Scheme 3.7-4).



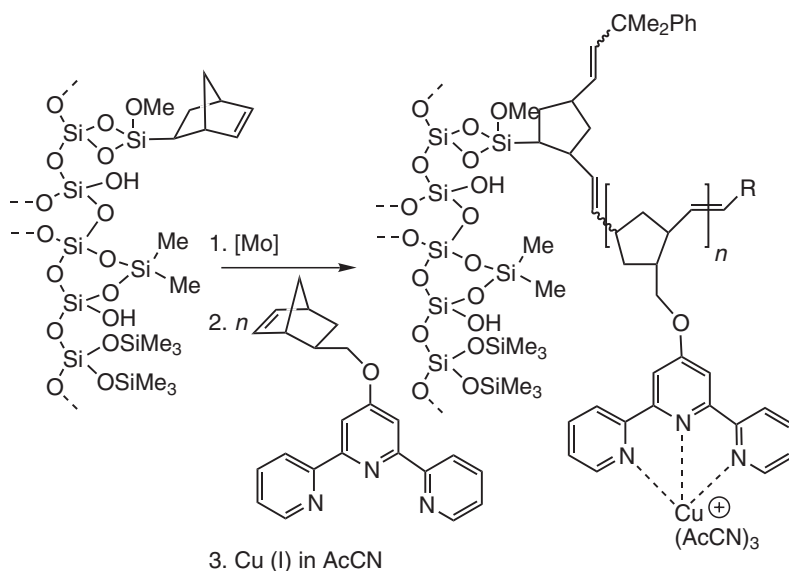
Scheme 3.7-4. Synthesis of octamethylferrocene-derived silica support used for the separation of oligonucleotides.



Scheme 3.7-5. Surface grafting of *N,N*-dipyrid-2-ylnorborn-2-en-5-ylcarbamide on silica.

(dT₁₂–dT₁₈). As outlined above, *N,N*-dipyrid-2-ylnorborn-2-en-5-ylcarbamide can be polymerized in a living manner using well-defined Schrock initiators [14]. Thus, a class VI living system [38] was accomplished with $\text{Mo}(\text{N}-2,6\text{-}i\text{-Pr}_2\text{-C}_6\text{H}_3)(\text{CHCMe}_2\text{Ph})(\text{CMe}(\text{CF}_3)_2)_2$. This monomer was grafted on norborn-2-ene surface functionalized silica, using a grafting-from approach to generate tentacles of poly(*N,N*-dipyrid-2-ylnorborn-2-en-5-ylcarbamide) with a controlled degree of polymerization (DP), typically <50 (Scheme 3.7-5).

It is worth mentioning that the careful end capping of silica with a mixture of ClSiMe_3 and Cl_2SiMe_2 eliminates any initiator deterioration caused by the interaction with the silanol groups. In addition, complete reaction of the initiator with the support, as evidenced by the absence of any soluble polymer, was observed [33]. Not surprisingly, $\text{Cl}_2\text{Ru}(\text{CHPh})(\text{PCy}_3)_2$ was not capable of polymerizing *N,N*-dipyrid-2-ylnorborn-2-en-5-ylcarbamide or its 7-oxa analogue due to an irreversible coordination of the ligand to the ruthenium core. Palladium loading of the supports was accomplished simply by reaction with H_2PdCl_4 . Within a few hours, a quantitative reaction was observed that resulted in slightly yellow-colored supports. Values of 0.28 mmol Pd g^{−1} and 0.08 mmol Pd g^{−1}, respectively, were achieved. The corresponding supports were again successfully used in a variety of Heck reactions, including slurry reactions under standard as well as microwave conditions. Removal of the support was again accomplished by filtration. In particular, the use of microwave led to a drastic reduction of reaction times, which is of particular interest for applications in high-throughput screening (HTS). TOFs were typically in the range of 0.1–0.3 s^{−1}. Alternatively, silica-based materials were used as reaction columns as employed in HTS machines. Such columns were loaded with the substrates of interest and, after complete reaction, were simply eluted with a suitable solvent leading the catalyst behind and analyzed by a high-



Scheme 3.7-6. Surface grafting of 4'-(norborn-2-en-5-ylmethylenoxy)terpyridine on silica.

throughput method, e.g., GC-MS. Quantitative conversion was achieved with iodoarenes, while even activated bromarenes require prolonged reaction times. Finally, catalyst-filled cartridges were realized where the surface-derivatized silica was packed into stainless steel columns. These devices were used in reactions as flow-through columns. As for monolith-based supports (*vide infra*), a constant conversion of iodobenzene with styrene (70–80%) was observed over several hours. TOFs were in the range of $0.06\text{--}0.07\text{ s}^{-1}$. Nevertheless, this value was clearly lower than that obtained with monolithic columns, illustrating the superiority of the latter ones (*vide infra*). In all these experiments, irrespective of the application, only minor amounts of Pd, typically less than 2.5%, were leached into the reaction mixture [47]. Finally, the ROMP of 4'-(norborn-2-en-5-ylmethylenoxy)terpyridine was described by our group. It fulfilled the requirements of a class V living system [38]. The corresponding surface-grafted support was prepared by applying a grafting-from approach as described above [33] (Scheme 3.7-6).

Loading with Cu(I) afforded the desired ATRP support [18, 48–50]. Typical metal loadings were in the range of 15 mmol g^{-1} . Polystyrene (PS) prepared under ATRP conditions with these supports showed comparably low polydispersities ($\text{PDI} = 1.55\text{--}1.77$). The ATRP system consisted of a metal center with one terpyridyl and presumably three acetonitrile ligands, which were at least in part substituted by monomer. Consequently, in contrast to standard systems [51], the equilibrium $\text{M}^{n+} \rightleftharpoons \text{M}^{n+1}$ in this type of reaction did not require conformational changes or dissociation of a terpyridyl ligand. Therefore, polymerization proceeded comparably quickly within 2 h. Unfortunately, presumably to unfavorable equilibria involving the dormant species, polymer yields were low (<35%).

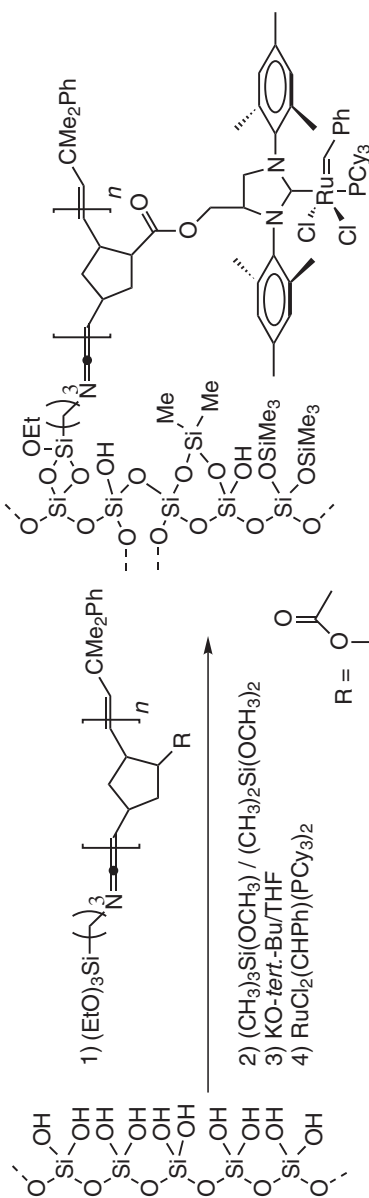
The capability of ROMP of polymerizing even complex functional monomers was demonstrated by the fact that the cationic NHC precursor 1,3-di(1-mesityl)-4-[[[bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]oxy]methyl]-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate was polymerized using both ruthenium- and molybdenum-based initiators. Thus, reaction of this monomer with $\text{Cl}_2\text{Ru}(\text{CHPh})(\text{PCy}_3)_2$ in methylene chloride at 45 °C resulted in complete consumption of the initiator and formation of an oligomer with a DP of 7. Alternatively, polymerizations with the Schrock initiator $\text{Mo}(N\text{-}2,6\text{-}i\text{-Pr}_2\text{-C}_6\text{H}_3)(\text{CHCMe}_2\text{Ph})(\text{OCMe}(\text{CF}_3)_2)_2$ [52] were performed in methylene chloride at ambient temperature. The theoretical DP of 7 was in excellent accordance with a DP of 7 ± 1 found via end-group analysis using ^1H -NMR. An end group suitable for oligomer grafting on silica was introduced by reacting the living polymer with an excess of ω -(triethoxysilyl)propylisocyanate (Scheme 3.7-7).

Next, telechelic oligo-(1,3-di(1-mesityl)-4-[[[bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]oxy]methyl]-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate) was reacted with silica. Reaction of the grafted supports with $\text{KO}\text{-}t\text{Bu}$ in THF at -30°C yielded the free carbene, which was subsequently reacted with $\text{Cl}_2\text{Ru}(\text{CHPh})(\text{PCy}_3)_2$ to yield the immobilized second-generation Grubbs catalyst [53]. The ruthenium content of the solution as measured by inductively coupled plasma-optical emission spectroscopy (ICP-OES) revealed catalyst loadings of 0.1–0.5 weight-%. RCM carried out with diethyl diallylmalonate (DEDAM) as a benchmark gave TONs ≤ 80 for a stirred batch, which is comparable to homogeneous systems. No catalyst bleeding was observed, thus offering access to virtually metal-free products. Identical protocols using Si/SiO_2 surface-bound norborn-2-enesilanes were also described later for the preparation of surface-bound thin polymer films by other groups [54].

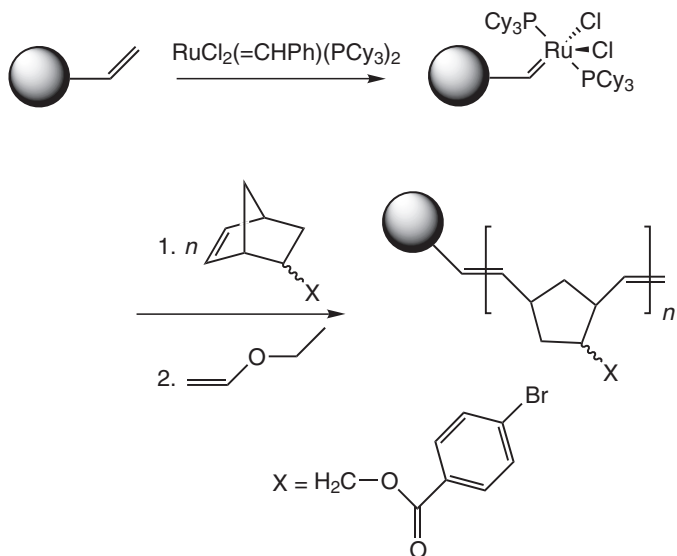
Barrett and coworkers reported on the synthesis of ROMP spheres for use in combinatorial chemistry [55]. These were synthesized by reaction of vinyl-PS-DVB with a low degree of cross-linking with $\text{Cl}_2\text{Ru}(=\text{CHPh})(\text{PCy}_3)_2$ to form the immobilized catalytic species. Finally, reaction with norborn-2-en-5-ylmethyl 4-bromobenzoate gave the corresponding support with loadings up to 3 mmol of functional monomer per gram resin (Scheme 3.7-8). Swelling properties were similar to those materials prepared by ring-opening metathesis precipitation polymerization.

In an identical approach, Grubbs et al. reported on the surface modification of $\text{Si}(\text{III})$. Conversion of surface Si-H into Si-allyl groups allowed pursuit of the grafting-from approach summarized in Scheme 3.7-9 [56].

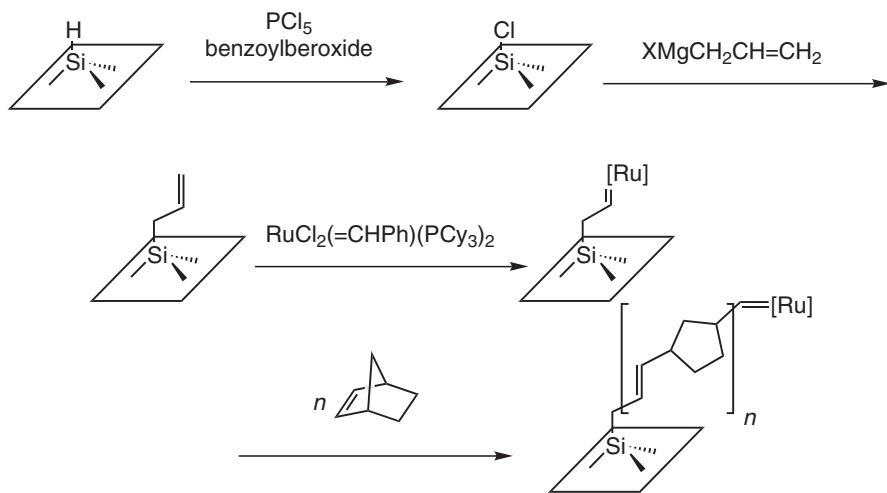
Similarly, Emrick and Coughlin et al. reported on the synthesis of cadmium selenide-polyolefin composites. A vinylbenzyl-derivatized phosphine oxide was physisorbed onto the cadmium selenide particles. Subsequent reaction with first- or second-generation Grubbs initiators followed by addition of cyclooctene, 7-oxanorborn-5-ene-2,3-dicarboxylic anhydride, dicyclopentadiene, or *N*-methyl-7-oxanorborn-5-ene-2,3-dicarboxylimide resulted in the desired surface modification and formation of the composite, which was proposed to possess interesting solution and electronic properties (Scheme 3.7-10) [57].



Scheme 3.7-7. Grafting of isocyanate-terminated poly(3-di(1-mesityl)-4-[[bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]oxymethyl]-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate) on silica and generation of the immobilized second-generation Grubbs catalyst.

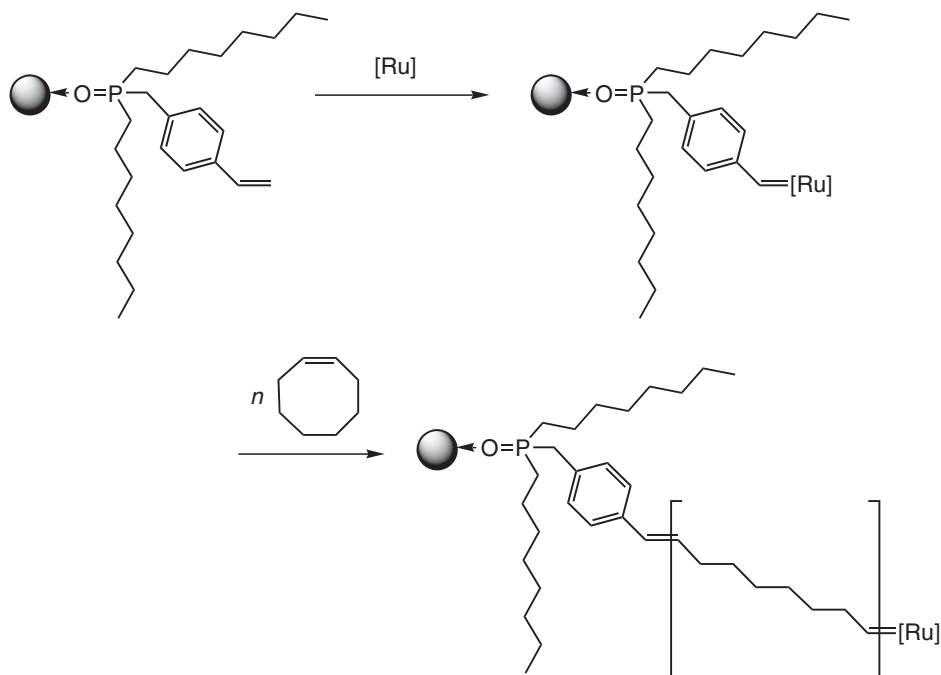


Scheme 3.7-8. Synthesis of ROMP spheres used for combinatorial chemistry.



Scheme 3.7-9. Grafting from approach developed for the surface functionalization of Si.

Recently, Caster et al. described the surface modification of multifilament fibers such as nylon or Kevlar [58]. Both coating techniques using preformed ROMP-based polymers and process contact metathesis polymerization (CMP), initially described by Grubbs et al. [59], were used. The latter comprised a procedure in which the initiator was physisorbed onto the surface of a substrate and fed with a ROMP active monomer that finally encapsulated the substrate. Such modified fibers showed improved adhesion to natural rubber elastomers.



Scheme 3.7-10. Cd–Se polymer composite prepared by Emrick and Coughlin et al.

3.7.4

Coating Techniques

Coating techniques offer straightforward access to cheap functional materials. These materials are generally prepared by depositing a more or less homogeneous polymer layer on the support of choice. Though such surface-coated materials are easy to make and are highly stable versus acids or bases, the inhomogeneous polymer distribution [60–62] and the restricted access to the catalytic centers, in particular in the case where these are located within micro- and mesopores, certainly present an impediment. In order to investigate the general applicability of ROMP-based polymers to these coating techniques, homopolymers of 7-oxanorborn-2-ene-5,6-dicarboxylic anhydride and block copolymers of this monomer with NBE were prepared and coated onto various silica supports [63]. Although, as described for other coatings, high-surface-area silica ($\sigma > 400 \text{ m}^2 \text{ g}^{-1}$) in particular suffered from significant loss in pore volume, pH-stable materials suitable for analytical and preparative scale ion chromatography were prepared [63]. Because of their peculiar properties, they were also used for the separation of flavonoids [64]. Even more interesting, the chelating properties of the *cis*-configured poly(succinic acid) for rare earth elements (REEs) were enhanced by the presence of the oxygen in the furan ring resulting from ROMP. In combination

with the pressure-stable silica support, a sorbent capable of the off- and online SPE-RP-ion-pair HPLC of lanthanides was developed. This sorbent allowed the quantitative and selective extraction of lanthanides present in complex mixtures such as rock digest of granite or basaltic rock, thus offering access to the quantification of REEs within a concentration range of $7.5 \mu\text{mol l}^{-1}$ to 1.5 pmol l^{-1} [12, 65]. The lower limit was determined by using the radioactive REE isotopes Pm-147 and Eu-152 [66].

Complementary to the ring-opening metathesis precipitation and grafting techniques, the synthesis of heterogeneous catalytic supports based on poly-(*N,N*-dipyrid-2-yl-norborn-2-en-5-yl-carbamide) deposited onto silica was accomplished by applying standard coating techniques [63]. Loading with Pd resulted in a support containing 0.02 mmol Pd. In general, the amounts of metal immobilized on silica were sufficiently high for any of the applications of interest. Slurry-type Heck reactions were successfully carried out under both standard and microwave conditions. In addition, these materials were filled in cartridges and used in the form of reaction columns [47].

Similar to the synthesis of Heck supports, silica was treated with solutions of poly(4'-(norborn-2-en-5-yl-methylenoxy)terpyridine) under evaporative conditions. Reaction with $\text{CuBr} \times \text{Me}_2\text{S}$ and $\text{Cu}(\text{OAc})_2 \times \text{H}_2\text{O}$, respectively, gave the corresponding Cu-loaded supports. As observed for grafted ATRP supports, the monoligated initiator resulted in comparably fast polymerizations. Using this system, PS was prepared up to a M_w of 80,000. Again, polymer yields were in the range of 35%. The polymers were virtually metal free, as determined by atom absorption spectroscopy (AAS), which revealed a metal content of less than 100 ng g^{-1} [18, 48–50].

Complementary to the above-mentioned grafting approach, coating techniques [63] using oligo-(1,3-di(1-mesityl)-4-[[bicyclo[2.2.1]hept-5-en-2-yl-carbonyl]oxy]-methyl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate) were applied, leading to a surface-derivatized silica 60 containing 0.09 mmol of NHC precursor. Conversion into the initiator was carried out as described for the grafted analogue, resulting in a support containing $4.1 \mu\text{mol}$ ruthenium g^{-1} . Good results were obtained with these coated supports in the RCM of DEDAM and 1,7-octadiene. Thus, TONs were 210 and 55, respectively, for these compounds under batch conditions. In all cases, ruthenium measurements by means of ICP-OES revealed quantitative retention of the original amount of ruthenium at the support within experimental error, thus offering an attractive access to metal-free products [53].

3.7.5

Monolithic Supports

Monolithic separation media have evolved as a successful “joint venture” between material and separation science. Based on theoretical reflections, the common idea was to produce a support with a high degree of continuity that should meet the

requirements for fast yet highly efficient separations [67, 68]. The first experiments in this direction were carried out in the 1960s and 1970s [69, 70], yet it took some 20 years to adapt this new technology for the area of heterogeneous catalysis. During their evolution, these supports, usually referred to as monolithic supports, continuous beds, or rigid rods [70], were successfully used in liquid chromatography, including micro-separation techniques [71–77], capillary electrochromatography, and solid-phase extraction (SPE) [78], focusing on medium- and high-molecular-mass biopolymers [79] and even on low-molecular-mass analytes [80–83]. Quite recently, i.e., in 2001, our group developed a ROMP-based synthesis for these types of materials [84–93] and described the use of these supports in heterogeneous catalysis [47, 92].

3.7.5.1

Basics and Concepts

Generally speaking, the term “monolith” applies to any single-body structure containing interconnected repeating cells or channels. Such materials may be metallic or prepared from inorganic mixtures, e.g., by a sintering process to form ceramics [94], or from organic compounds, usually by a cross-linking polymerization [95, 96]. In this chapter, the terms “monolith” or “rigid rod” shall comprise cross-linked, organic materials that are characterized by a defined porosity and that support interactions/reactions between this solid and the surrounding liquid phase. Besides advantages such as lower backpressure and enhanced mass transfer [97, 98], the ease of fabrication as well as the many possibilities in structural alteration need to be mentioned.

Until now, a considerable variety of functionalized and non-functionalized monolithic materials based on either organic or inorganic polymers have been available. While inorganic monoliths are usually prepared from silica precursors (i.e., $\text{Si}(\text{OR})_4$) via sol-gel techniques [80–83], organic continuous beds have mostly been prepared from methacrylates or poly(styrene-*co*-divinylbenzene) [95, 99–102] applying almost exclusively free-radical polymerization. Profound insights into the technology of both sol-gel and free-radical polymerization-based monoliths can be found in books particularly dedicated to this subject [103]. Despite the comparably poor control over free-radical polymerization-based systems, the porosity and microstructure of monolithic materials have been varied successfully [95]. In contrast to the free-radical process, our group confirmed the general applicability of a transition metal-based polymerization technique such as ROMP to the synthesis of high-performance monolithic separation media. Due to the broad applicability of ROMP and the good definition of the resulting materials, we investigated to what extent this transition metal-catalyzed polymerization could be used for the synthesis of monolithic polymers [85]. We found that this could be accomplished by generating a continuous matrix by ring-opening metathesis copolymerization of suitable monomers with a cross-linker in the presence of porogenic solvents within a device (column).

3.7.5.2

Manufacture of Metathesis-Based Monolithic Supports

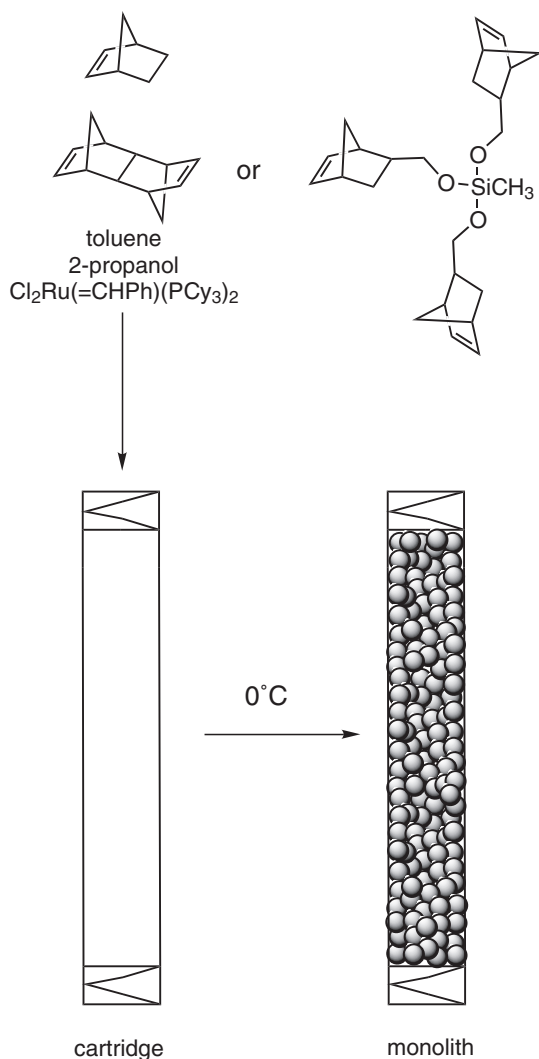
The choice of the suitable initiator represents an important step in creating a well-defined polymerization system in terms of initiation efficiency and control over propagation. Only in the case where a quantitative and fast initiation occurs can the entire system be designed on a stoichiometric base. This is of enormous importance, as for control of microstructure the composition of the entire polymerization mixture needs to be varied within small increments. The catalyst needs to be carefully selected from both chemical and practical points of view. Generally, Schrock and Grubbs systems, both highly active in the ROMP of strained functionalized olefins, can be used. Because the preparation and, in particular, derivatization of ROMP-based rigid rods require some handling that can hardly be performed under an inert atmosphere, the less oxygen-sensitive and less reactive ruthenium-based Grubbs-type initiators were used. Since $\text{Cl}_2(\text{PPh}_3)_2\text{Ru}(=\text{CHPh})$ turned out to be too unreactive, $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(=\text{CHPh})$ was used. In order to avoid any uncontrolled, highly exothermic reactions, second-generation Grubbs catalyst were not used. Among the possible combinations of monomers and cross-linkers such as NBE, norbornadiene (NBDE), dicyclopentadiene (DCPD), 1,4,4a,5,8,8a-hexahydro-1,4,5,8-*exo-endo*-dimethanonaphthalene (DMN-H6), tris(norborn-2-en-5-ylmethylenoxy)methylsilane ($\text{NBE-CH}_2\text{O})_3\text{SiCH}_3$), and 1,4a,5,8,8a,9,9a,10,10a-decahydro-1,4,5,8,9,10-trimethanoanthracene, the copolymerization of NBE with DMN-H6 or $(\text{NBE-CH}_2\text{O})_3\text{SiCH}_3$ in the presence of two porogenic solvents, e.g., 2-propanol and toluene, with $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(=\text{CHPh})$ worked best (Scheme 3.7-11).

3.7.5.3

Microstructure of Metathesis-Based Rigid Rods

In order to understand monolithic supports and the effects of polymerization parameters, a brief description of the general construction of a monolith in terms of microstructure, backbone, and relevant abbreviations is given in Figure 3.7-3 [84, 85]. As can be deduced therefrom, monoliths consist of interconnected microstructure-forming microglobules, which are characterized by a certain diameter (d_p) and microporosity (ε_p). In addition, the monolith is characterized by an inter-microglobule void volume (ε_z), which is mainly responsible for the backpressure at a certain flow rate.

The volume fractions of both micropores (ε_p) and voids (intermicroglobule porosity, ε_z) represent the total porosity (ε_t). This value, indicating a percentage of pores in the monolith, together with the pore-size distribution that can be calculated from inverse size exclusion chromatography (ISEC) data [4] or from mercury intrusion [104], on the one hand directly translates into a total pore volume V_p , expressed in ml g^{-1} and, on the other hand, allows calculation of the specific surface area σ , expressed in $\text{m}^2 \text{g}^{-1}$. In order to design monolithic supports for different tasks, the influence of all variables, i.e., components of the polymerization



Scheme 3.7-11. Monolith synthesis.

mixture (NBE, DMN-H6 or NBE-CH₂O)₃SiCH₃, solvents, free phosphine and initiator, as well as temperature), on microstructure formation was investigated. The relative ratios of all components, i.e., NBE, DMN-H6, porogens, and catalyst, allowed broad variations in the microstructure of the monolithic material, including structures ideal for heterogeneous catalysis. In summary, the volume fraction of the interglobular void volume (ε_z) and total porosity (ε_t) was varied within a range of 0–50% and 50–80%, respectively. Figure 3.7-4 illustrates some of the microstructures that were generated.

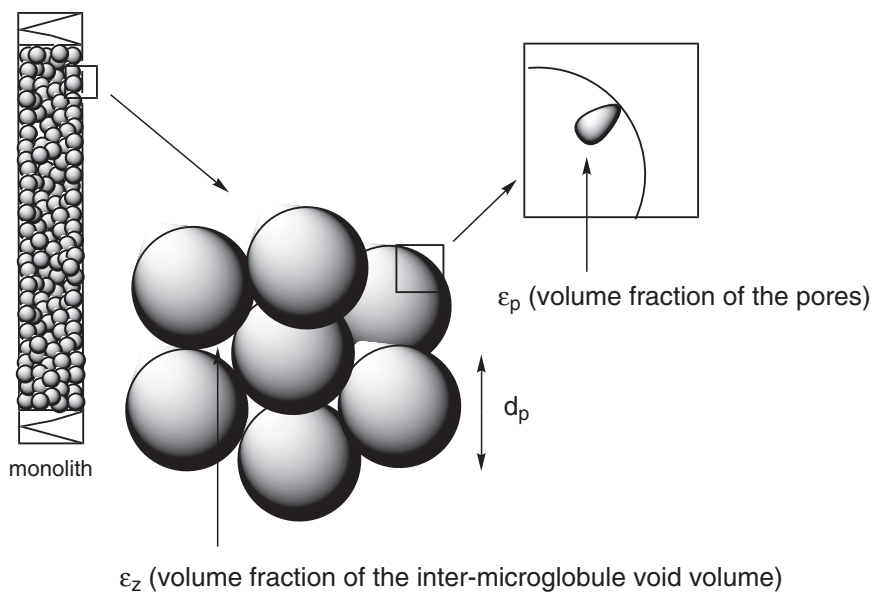


Fig. 3.7-3. General construction of a monolith.

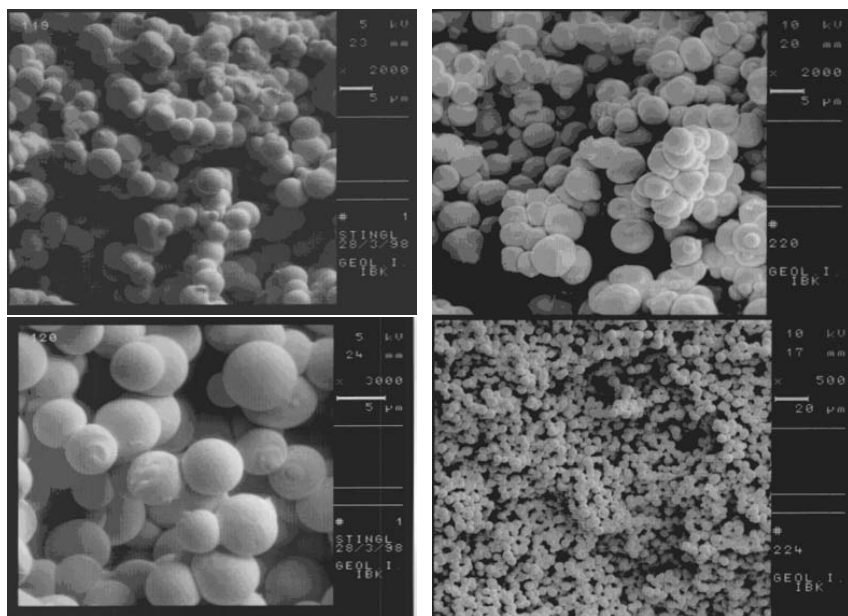
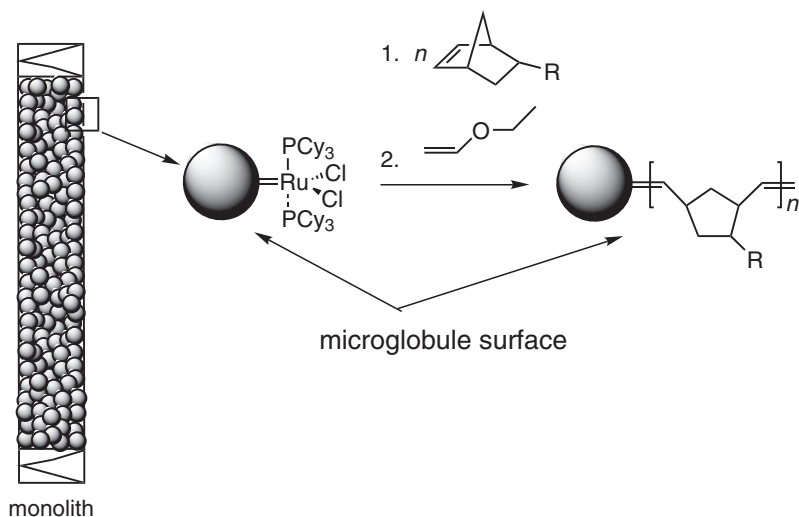


Fig. 3.7-4. Representative microstructures of monoliths used in separation science and heterogeneous catalysis.



Scheme 3.7-12. Surface functionalization of a monolith.

3.7.5.4

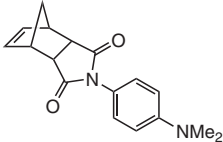
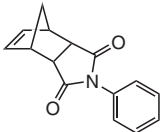
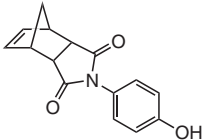
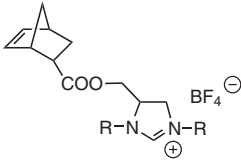
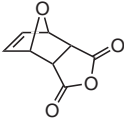
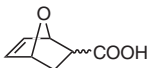
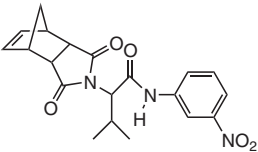
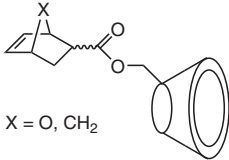
Functionalization, Metal Removal, and Metal Content

Using the ROMP-based protocol, functionalization can be achieved conveniently. In particular the “living” character [38, 105] of ruthenium-catalyzed polymerizations [106–109] and the high tolerance of the catalytic system towards different functional monomers made the ROMP approach very attractive. In fact, the active ruthenium sites could be used for derivatization after rod formation was complete. ICP-OES-based investigations revealed that more than 98% of the initial amount of initiator was located at the microglobule surface after microstructure formation [92]. Using the initiator covalently bound to the surface, functional monomers were grafted onto the monolith surface by simply passing solutions thereof through the mold (Scheme 3.7-12) [84, 85].

Since no cross-linking can take place, tentacle-like polymer chains attached to the surface were formed. In addition, microglobules were designed in such a way that their pore size was <1.2 nm, which basically restricted functionalization to their surface [88]. The degree of this graft polymerization of functional monomers varies within almost 2 orders of magnitude, depending on their ROMP activity. This approach offered multiple advantages. First, the structure of the “parent” monolith was not affected by the functional monomer and could be optimized regardless of the functional monomer used later. Secondly, solvents other than the porogens (e.g., methylene chloride, DMF) can be used for the *in situ* derivatization, depending on the solubility of the monomer. An overview of the different monomers that have already been grafted is given in Table 3.7-3.

Due to the fact that the initiator was almost quantitatively located at the surface of the microglobules, the efficiency of metal removal from the monolith after

Tab. 3.7-3. Functional monomers used for surface grafting of monolithic supports.

<i>monomer</i>	<i>mmol/g</i>
	0.26
	0.22
	0.06
	0.002
	0.2
	0.14
	0.03
 X = O, CH ₂	—

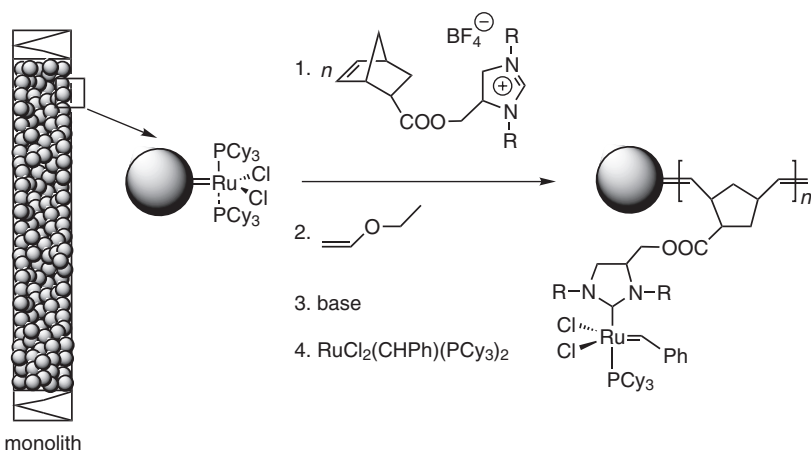
polymerization was high. Investigations revealed that the remaining ruthenium-concentrations after capping with ethylvinyl ether were below $10 \mu\text{g g}^{-1}$, corresponding to a metal removal of more than 99.8%.

3.7.5.5

Applications of Functionalized Metathesis-Based Monoliths in Catalysis

Grafted supports for ring-closing metathesis and related reactions In heterogeneous catalysis, one wants to combine the general advantages of homogeneous systems such as high definition, activity, etc., with the advantages of heterogeneous catalysis such as increased stability, ease of separation, and recycling. So far, monolithic catalytic media have basically been restricted to metal oxides, porous metals, and certain polysaccharides [110]. The first successful use of metathesis-based monolithic media for heterogeneous catalysis was accomplished by using these supports as carriers for Grubbs-type initiators based on *N*-heterocyclic carbenes (NHC ligands) [111, 112]. In order to generate sufficient porosity, monoliths with a suitable microporosity (40%) and microglobule diameter ($1.5 \pm 0.5 \mu\text{m}$) were synthesized. Consecutive *in situ* derivatization was successfully accomplished using a mixture of norborn-2-ene and a polymerizable NHC precursor (Scheme 3.7-13) [21, 92, 113–115].

The use of norborn-2-ene drastically enhanced grafting yields for the functional monomer. Using this setup, tentacles of copolymer with a degree of oligomerization of the functional monomer of 2–5 were generated. The free NHC necessary for catalyst formation was generated simply by using a strong base such as 4-dimethylaminopyridine (DMAP). In a last step, excess base was removed by extensive washing, and the catalyst was immobilized/formed by passing a solution of $\text{Cl}_2\text{Ru}(\text{CHPh})(\text{PCy}_3)_2$ over the rigid rod. Loadings of up to 1.4% of Grubbs cata-

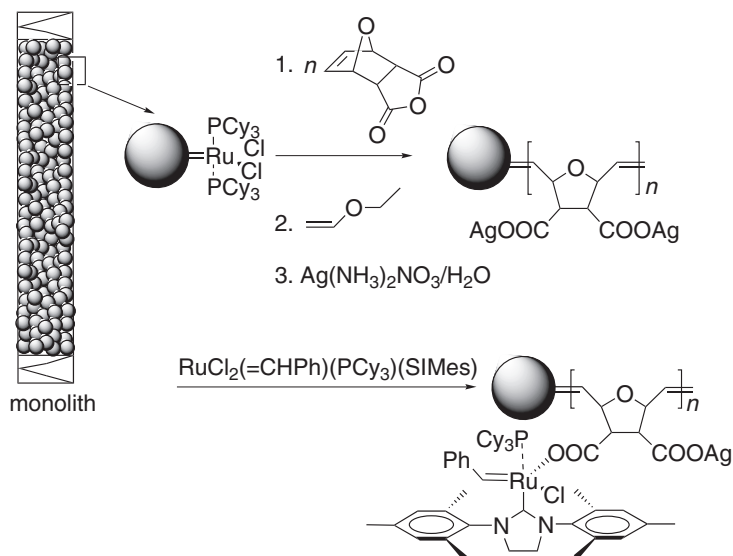


Scheme 3.7-13. Synthesis of a monolith-supported second-generation catalyst immobilized via the NHC ligand.

lyst on NHC base were achieved. Monolith-immobilized metathesis catalysts prepared by this approach showed high activity in various metathesis-based reactions such as ROMP and RCM. The *cis/trans* ratios of polymers (90%) exactly corresponded to the ones found to be analogous with homogeneous systems. The use of chain-transfer agents (CTAs, e.g., *cis*-1,4-diacetoxybut-2-ene, diethyldiallylmalonate, 2-hexene) allowed the regulation of molecular mass, in particular in the case of cyclooctene. The presence of CTAs additionally enhanced the lifetime of the catalytic centers by reducing the average lifetime of the ruthenium methylidenes, thus allowing the prolonged use of these systems. Additionally, both the tentacle-type structure and the designed microstructure of the support reduced diffusion to a minimum. In a benchmark reaction with DEDAM, these properties directly translated into high average turnover frequencies (TOFs) of up to 0.5 s^{-1} , thus exceeding even the homogeneous analogue ($\text{TOF} = 0.07\text{ s}^{-1}$; $45\text{ }^{\circ}\text{C}$) [116].

Alternatively, monolith-supported second-generation Grubbs catalysts containing unsaturated (e.g., IMes) or saturated (e.g., SIMes) NHCs [117] can be prepared by a synthetic protocol summarized in Scheme 3.7-14. Surface derivatization of a monolith was carried out with 7-oxanorborn-2-enedicarboxylic anhydride followed by conversion of the grafted poly(anhydride) into the corresponding poly-silver salt. This silver salt was used for the halogen exchange with a broad variety of second-generation Grubbs catalysts, leading to the catalytic species shown in Scheme 3.7-14. In the benchmark reaction with DEDAM, TONs up to 830 were achieved [114, 118].

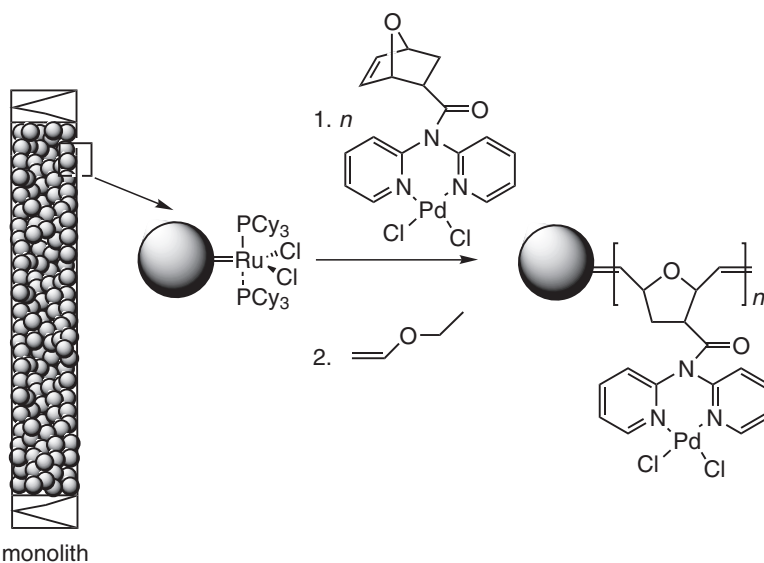
All monolith-based catalytic systems summarized here were successfully used as pressure-stable catalytic reactors. Bleeding was virtually suppressed, leading



Scheme 3.7-14. Synthesis of a monolith-supported second-generation catalyst immobilized via a carboxylate ligand.

even in RCM to basically ruthenium-free products, with a ruthenium content far below 0.1%.

Poly-(*N,N*-dipyrid-2-yl-7-oxanorborn-2-en-5-ylcarbamido-PdCl₂)-grafted monolithic supports for Heck reactions As outlined for the synthesis of heterogeneous metathesis catalysts, a grafting-from approach was used for the immobilization of dipyridylamide ligands. Due to the incompatibility of ruthenium and pyridyl ligands, a completely new approach was elaborated for monolith functionalization with these ligands. Since the nitrogen lone pair needed to be prevented from coordinating to the ruthenium core, the preformed complex, *N,N*-dipyrid-2-yl-7-oxanorborn-2-en-5-ylcarbamido palladium dichloride, was grafted onto a monolith using norborn-2-ene as a comonomer (Scheme 3.7-15).



Scheme 3.7-15. Synthesis of a monolith-supported Pd catalyst.

Grafted monoliths contained 7 μmol (0.07%) Pd. In a model reaction between styrene and iodobenzene, TOFs of 1.2–1.6 s^{-1} were found. These figures clearly exceed those obtained with supports prepared by ring-opening metathesis precipitation polymerization, which gave TOFs of 0.35 s^{-1} in an identical reactions [15]. Pd leaching was generally low (2.2% total over 10 h). Alternatively, if used as a cartridge, amounts of reactants typical in combinatorial chemistry (50–100 mg in total) were converted in satisfactory yields (<80%) [47].

Poly-(*N,N*-dipyrid-2-yl-7-oxanorborn-2-en-5-ylcarbamido-PdCl₂)-coated monolithic supports for Heck reactions Alternatively, a coating procedure using poly(*N,N*-di(pyrid-2-yl)norborn-2-ene-5-ylcarbamide) followed by reaction with H_2PdCl_4 was developed and was found to be applicable to the modification of monolithic

supports. Monolithic supports were surface coated with poly(*N,N*-di(pyrid-2-yl)-norborn-2-ene-5-ylcarbamide) [84, 85, 88, 92]. Subsequent loading with Pd(II) resulted in supports containing 0.031 mmol (0.33%) Pd. Such supports were used in the form of closed cartridges for HTS or as flow-through reactors. Model reactions between iodobenzene and styrene were carried out in tributylamine without any additional solvent using a flow-through setup. At temperatures of 140 °C and 170 °C, respectively, solvent-free mixtures of iodobenzene, styrene, and NBu_3 were constantly converted into stilbene over a period of 3 h. Constant TOFs of 0.3–0.4 s^{-1} were found [47], which were comparable to those obtained with supports prepared by ring-opening metathesis precipitation polymerization (TOF = 0.35 s^{-1}) [15].

Monolithic supports for separation science Due to the pure hydrocarbon backbone, monoliths prepared from NBE and DMN-H6 are strongly hydrophobic. Nevertheless, the resulting materials significantly differ from PS-DVB-based resins, in that the latter contains aromatic systems that are capable of forming π -stacks with analytes possessing aromatic groups. The impressive separation capabilities have been demonstrated by the fast separation of biologically relevant compounds such as proteins, double stranded (ds) DNA, oligonucleotides, and phosphorothioate oligodeoxynucleotides. As an example, the separation of 10 proteins was accomplished within less than 90 s at flow rates of 2 ml min^{-1} . Such separation performance at high flow rates gives an illustration of the fast mass transfer that can be achieved [41, 84–86]. Furthermore, 20 base pairs of ds DNA were separated on both standard (i.e., 3×100 mm) and microanalytical (200 mm i.d.) monolithic columns [87, 119].

While non-functionalized monolithic media are useful supports for the separation of biomolecules via a reversed-phase (RP) mechanism, functionalized analogues are highly attractive for other separation problems that might be solved by other separation mechanisms, e.g., chiral chromatography, ion chromatography, etc. Using a β -cyclodextrin-grafted monolith, proglumide (a β -blocker) was separated in less than 3 min, which clearly underlines the potential of this type of chemistry in many areas of separation science.

Monolithic supports for size-exclusion chromatography Starting from monolithic norborn-2-ene-based systems with discontinuous porosity [84–87], we developed monolithic beds with continuous porosity for use in SEC [88]. In order to generate maximum long-term stability, a mixture of DMN-H₆ and $(\text{NBE-CH}_2\text{O})_3\text{SiCH}_3$ was used. On the one hand, such a mixture gave access to sufficiently cross-linked and therefore long-term stable monoliths; on the other hand, they possessed favorable pore-size distributions resulting from the use of DMN-H₆. Monoliths showed a rationally intermediate pore-size distribution with about 50% of the pores in the micropore region below 12.5 Å. In addition to their good and reproducible performance, the most important feature of these supports was the significant reduction in separation times (less than 5 min for molecular weights of 2,000–1,300,000 g mol^{-1}) that was achieved. In combination with their comparably small

size (250×5 mm), this offered access to the high-throughput analysis of polymer samples, e.g., obtained from combinatorial polymerization catalyst screening.

3.7.6

Conclusions, Summary, and Outlook

Metathesis-based polymerization techniques have certainly found their place in materials science. This has been made possible by adding well-defined and tolerant initiators to the array of existing polymerization systems. With these initiators, in particular ROMP and 1-alkyne polymerization have had an enormous impact on the development of both surface-modified and polymeric materials. Applications in catalysis and separation science have been added to the more “traditional” ones in optics and electronics. The ongoing developments in organometallic chemistry, polymer chemistry, and, in particular, metathesis polymerization will certainly result in the permanent improvement of existing systems and techniques as well as in new applications in many areas of chemistry and materials science.

Acknowledgments

Our work was supported by grants from the Austrian Science Fund (projects P-12963-GEN, START Y-158), the Österreichische Nationalbank (project 789), the University of Innsbruck, the Industriellenvereinigung Tirol, and the European Commission (contracts F14W-CT96-0019 and FIS 1999-00130). I wish to thank all my students and postgraduate students involved in the work described in this chapter for their dedication and enthusiasm.

References

- 1 E. ÅRSTAD, A. G. M. BARRETT, B. T. HOPKINS, J. KÖBBERLING, *Org. Lett.* **2002**, *4*, 1975–1977.
- 2 R. R. SCHROCK, *Acc. Chem. Res.* **1986**, *19*, 342–368.
- 3 I. HALÁSZ, K. MARTIN, *Ber. Bunsenges. Phys. Chem.* **1975**, *79*, 731–732.
- 4 I. HALÁSZ, K. MARTIN, *Angew. Chem.* **1978**, *90*, 954–961; *Angew. Chem. Int. Ed.* **1978**, *17*, 901–909.
- 5 M. R. BUCHMEISER, N. ATZL, G. K. BONN, *J. Am. Chem. Soc.* **1997**, *119*, 9166–9174.
- 6 D. AMBROSE, J. S. FRITZ, M. R. BUCHMEISER, N. ATZL, G. K. BONN, *J. Chromatogr. A* **1997**, *786*, 259–268.
- 7 K. EDER, M. R. BUCHMEISER, G. K. BONN, *J. Chromatogr. A* **1998**, *810*, 43–52.
- 8 G. SEEGER, M. R. BUCHMEISER, G. K. BONN, T. BERTSCH, *J. Chromatogr. A* **1998**, *809*, 121–129.
- 9 C. G. HUBER, M. R. BUCHMEISER, *Anal. Chem.* **1998**, *70*, 5288–5295.
- 10 M. R. BUCHMEISER, R. TESSADRI, Austrian Pat. Appl. A 1132/97 (020797)
- 11 M. R. BUCHMEISER, R. TESSADRI, G. SEEGER, G. K. BONN, *Anal. Chem.* **1998**, *70*, 2130–2136.
- 12 M. R. BUCHMEISER, *Rev. Anal. Chem.* **2001**, *20*, 161–1784.
- 13 M. R. BUCHMEISER, F. SINNER, R. TESSADRI, G. K. BONN, Austrian Pat. Appl. AT 405 056B (010497)
- 14 F. SINNER, M. R. BUCHMEISER, R. TESSADRI, M. MUPA, K. WURST, G. K. BONN, *J. Am. Chem. Soc.* **1998**, *120*, 2790–2797.

- 15 M. R. BUCHMEISER, K. WURST, *J. Am. Chem. Soc.* **1999**, 121, 11101–11107.
- 16 J. SILBERG, T. SCHAREINA, R. KEMPE, K. WURST, M. R. BUCHMEISER, *J. Organomet. Chem.* **2000**, 622, 6–18.
- 17 M. R. BUCHMEISER, T. SCHAREINA, R. KEMPE, K. WURST, *J. Organomet. Chem.* **2001**, 634, 39–46.
- 18 M. R. BUCHMEISER, R. KRÖLL, K. WURST, T. SCHAREINA, R. KEMPE, C. ESCHBAUMER, U. S. SCHUBERT, in *Makromol. Symp. (Tailormade Polymers)*, Vol. 164 (Eds.: H.-J. P. ADLER, K.-F. ARNDT, D. KUCKLING, M. STAMM, B. VOIT AND T. WOLFF), 2001, pp. 187–196.
- 19 M. R. BUCHMEISER, in *NATO Science Series II. Mathematics, Physics and Chemistry*, Vol. 56 (Eds.: E. KHOSRAVI AND T. SZYMANSKA-BUZAR), Klywer, 2002, pp. 195–204.
- 20 M. R. BUCHMEISER, Austrian Patent Appl. AT 406 830 B (A 344/99, 020399)
- 21 M. R. BUCHMEISER, *Bioorg. Med. Chem. Lett.* **2002**, 12, 1837–1840.
- 22 E. LINDNER, T. SCHNELLER, F. AUER, H. A. MAYER, *Angew. Chem.* **1999**, 111, 2288–2309; *Angew. Chem. Int. Ed.* **1999**, 38, 2154–2174.
- 23 T. ARNAULD, A. G. M. BARRETT, R. SEIFRIED, *Tetrahedron Lett.* **2001**, 42, 7899–7901.
- 24 A. G. M. BARRETT, S. M. CRAMP, A. J. HENNESSY, P. A. PROCOPIOU, R. S. ROBERTS, *Org. Lett.* **2001**, 3, 271–273.
- 25 T. ARNAULD, A. G. M. BARRETT, B. T. HOPKINS, *Tetrahedron Lett.* **2002**, 43, 1081–1083.
- 26 A. G. BARRETT, S. M. CRAMP, R. S. ROBERTS, F. J. ZECRI, *Org. Lett.* **1999**, 1, 579–582.
- 27 T. ARNAULD, A. G. M. BARRETT, S. M. CRAMP, R. S. ROBERTS, F. J. ZÉCRI, *Org. Lett.* **2000**, 2, 2663–2666.
- 28 K. J. WATSON, J. ZHU, S. T. NGUYEN, C. A. MIRKIN, *J. Am. Chem. Soc.* **1999**, 121, 462–463.
- 29 K. J. WATSON, J. ZHU, S. T. NGUYEN, C. A. MIRKIN, *Pure & Appl. Chem.* **2000**, 72, 67–72.
- 30 M. WECK, J. J. JACKIW, R. R. ROSSI, P. S. WEISS, R. H. GRUBBS, *J. Am. Chem. Soc.* **1999**, 121, 4088–4089.
- 31 M. WU, S. A. O'NEILL, L. C. BROUSSEAU, W. P. MCCONNELL, D. A. SHULTZ, R. J. LINDERMAN, D. L. FELDHEIM, *Chem. Commun.* **2000**, 775–776.
- 32 M. R. BUCHMEISER, F. M. SINNER, PCT A 604/99 (070499), PCT/EP00/02 846, WO 00/61288
- 33 M. R. BUCHMEISER, F. SINNER, M. MUPA, K. WURST, *Macromolecules* **2000**, 33, 32–39.
- 34 M. R. BUCHMEISER, in *NATO Science Series II. Mathematics, Physics and Chemistry*, Vol. 56 (Eds.: E. KHOSRAVI AND T. SZYMANSKA-BUZAR), Klywer, 2002, pp. 205–215.
- 35 S. ITSUNO, K. UCHIKOSHI, K. ITO, *J. Am. Chem. Soc.* **1990**, 112, 8187–8188.
- 36 J. H. BABLER, K. P. SPINA, *Synth. Comm.* **1984**, 14, 1313–1319.
- 37 K. B. YOON, J. K. KOCHI, *J. Chem. Soc. Chem. Commun.* **1987**, 1013–1014.
- 38 K. MATYJASZEWSKI, *Macromolecules* **1993**, 26, 1787–1788.
- 39 B. MAYR, F. SINNER, M. R. BUCHMEISER, *J. Chromatogr. A* **2001**, 907, 47–56.
- 40 B. MAYR, H. SCHOTTENBERGER, O. ELSNER, M. R. BUCHMEISER, *J. Chromatogr. A* **2002**, 973, 115–122.
- 41 B. MAYR, M. R. BUCHMEISER, *J. Chromatogr. A* **2001**, 907, 73–80.
- 42 M. R. BUCHMEISER, R. R. SCHROCK, *Macromolecules* **1995**, 28, 6642–6649.
- 43 M. BUCHMEISER, *Macromolecules* **1997**, 30, 2274–2277.
- 44 M. R. BUCHMEISER, N. SCHULER, G. KALTENHAUSER, K.-H. ONGANIA, I. LAGOJA, K. WURST, H. SCHOTTENBERGER, *Macromolecules* **1998**, 31, 3175–3183.
- 45 M. R. BUCHMEISER, N. SCHULER, H. SCHOTTENBERGER, I. KOHL, A. HALLBRUCKER, *Designed Monomers & Polymers* **2000**, 3, 421–446.
- 46 K. EDER, E. REICHEL, H. SCHOTTENBERGER, C. G. HUBER, B. M. R., *Macromolecules* **2001**, 34, 4334–4341.
- 47 M. R. BUCHMEISER, S. LUBBAD, M. MAYR, K. WURST, *Inorg. Chim. Acta* **2003**, 345, 145–153.
- 48 U. S. SCHUBERT, C. S. ESCHBAUMER, C. SCHWAIG, P. ANDRES, R. M. KRÖLL, M. R. BUCHMEISER, German Pat. Appl. DE 100 13 305.3-44 (170300)

- 49 R. KRÖLL, C. ESCHBAUMER, U. S. SCHUBERT, M. R. BUCHMEISER, K. WURST, *Macromol. Chem. Phys.* **2001**, *202*, 645–653.
- 50 U. S. SCHUBERT, C. H. WEIDL, C. ESCHBAUMER, R. KRÖLL, M. R. BUCHMEISER, *Polym. Mater. Sci. Eng.* **2001**, *84*, 514–515.
- 51 K. MATYJASZEWSKI, J. XIA, *Chem. Rev.* **2001**, *101*, 2921–2990.
- 52 J. H. OSKAM, H. H. FOX, K. B. YAP, D. H. MCCONVILLE, R. O'DELL, B. J. LICHTENSTEIN, R. R. SCHROCK, *J. Organomet. Chem.* **1993**, *459*, 185–197.
- 53 M. MAYR, M. R. BUCHMEISER, K. WURST, *Adv. Synth. Catal.* **2002**, *355*, 712–719.
- 54 N. Y. KIM, N. L. JEON, I. S. CHOI, S. TAKAMI, Y. HAADA, K. R. FINNIE, G. S. GIROLAMI, R. G. NUZZO, G. M. WHITESIDES, P. E. LAIBINIS, *Macromolecules* **2000**, *33*, 2793–2795.
- 55 A. G. M. BARRETT, S. M. CRAMP, R. S. ROBERTS, *Org. Lett.* **1999**, *1*, 1083–1086.
- 56 A. JUANG, O. A. SCHERMAN, R. H. GRUBBS, N. S. LEWIS, *Langmuir* **2001**, *17*, 1321–1323.
- 57 H. SKAFF, M. F. ILKER, E. B. COUGHLIN, T. EMRICK, *J. Am. Chem. Soc.* **2002**, *124*, 529–5733.
- 58 K. C. CASTER, R. D. WALLS, *Adv. Synth. Catal.* **2002**, *344*, 764–770.
- 59 F. L. KLAVETTER, R. H. GRUBBS, *J. Am. Chem. Soc.* **1988**, *110*, 7807–7813.
- 60 A. KURGANOV, O. KUZMENKO, V. A. DAVANKOV, B. ERAY, K. K. UNGER, U. TRÜDINGER, *J. Chromatogr.* **1990**, *506*, 391–400.
- 61 M. HANSON, B. ERAY, K. UNGER, A. V. NEIMARK, J. SCHMID, K. ALBERT, E. BAYER, *Chromatographia* **1993**, *35*, 403.
- 62 M. R. BUCHMEISER, *J. Chromatogr. A* **2001**, *918/2*, 233–266.
- 63 M. R. BUCHMEISER, M. MUPA, G. SEEBER, G. K. BONN, *Chem. Mater.* **1999**, *11*, 1533–1540.
- 64 C. W. HUCK, M. R. BUCHMEISER, G. K. BONN, *J. Chromatogr. A* **2001**, *941*, 33–38.
- 65 M. R. BUCHMEISER, G. SEEBER, R. TESSADRI, *Anal. Chem.* **2000**, *72*, 2595–2602.
- 66 G. SEEBER, P. BRUNNER, M. R. BUCHMEISER, G. K. BONN, *J. Chromatogr. A* **1999**, *848*, 193–202.
- 67 N. B. AFEYAN, N. F. GORDON, I. MAZSAROFF, L. VARADY, S. P. FULTON, Y. B. YANG, F. E. REGNIER, *J. Chromatogr.* **1990**, *519*, 1.
- 68 N. B. AFEYAN, S. P. FULTON, F. E. REGNIER, *J. Chromatogr.* **1991**, *544*, 267–279.
- 69 M. KUBIN, P. SPACEK, R. CHROMECEK, *Collect. Czech. Chem. Commun.* **1967**, *32*, 3881–3887.
- 70 L. C. HANSEN, R. E. SIEVERS, *J. Chromatogr.* **1974**, *99*, 123–133.
- 71 K. HOSOYA, H. OHTA, K. YOSHIZOKA, K. KIMATAS, T. IKEGAMI, N. TANAKA, *J. Chromatogr. A* **1999**, *853*, 11–20.
- 72 A. MARUSKA, C. ERICSON, A. VÉGVÁRI, S. HJERTÉN, *J. Chromatogr. A* **1999**, *837*, 25–33.
- 73 I. GUSEV, X. HUANG, C. HORVÁTH, *J. Chromatogr. A* **1999**, *855*, 273–290.
- 74 Q. TANG, B. XIN, M. L. LEE, *J. Chromatogr. A* **1999**, *837*, 35–50.
- 75 R. ASIAIE, X. HUANG, D. FARNAN, C. HORVÁTH, *J. Chromatogr. A* **1998**, *806*, 251–263.
- 76 E. C. PETERS, M. PETRO, F. SVEC, J. M. J. FRÉCHET, *Anal. Chem.* **1997**, *69*, 3646–3649.
- 77 E. C. PETERS, M. PETRO, F. SVEC, J. M. J. FRÉCHET, *Anal. Chem.* **1998**, *70*, 2288–2295.
- 78 S. XIE, F. SVEC, J. M. J. FRÉCHET, *Chem. Mater.* **1998**, *10*, 4072–4078.
- 79 J. A. GERSTNER, R. HAMILTON, S. M. CRAMER, *J. Chromatogr.* **1992**, *596*, 173–180.
- 80 N. TANAKA, H. NAGAYAMA, H. KOBAYASHI, T. IKEGAMI, K. HOSOYA, N. ISHIZUKA, H. MINAKUCHI, K. NAKANISHI, K. CABRERA, D. LUBDA, *J. High Resol. Chromatogr.* **2000**, *23*, 111–116.
- 81 F. RABEL, K. CABRERA, D. LUBDA, *Int. Lab.* **2001**, *01/02*, 23–25.
- 82 K. CABRERA, K. SINZ, D. CUNNINGHAM, *Int. Lab. News* **2001**, *02*, 12–13.
- 83 K. CABRERA, D. LUBDA, H.-M. EGGENWEILER, H. MINAKUCHI, K. NAKANISHI, *J. High Resol. Chromatogr.* **2000**, *23*, 93–99.
- 84 F. SINNER, M. R. BUCHMEISER, *Macromolecules* **2000**, *33*, 5777–5786.

- 85 F. SINNER, M. R. BUCHMEISER, *Angew. Chem.* **2000**, 112, 1491–1494; *Angew. Chem. Int. Ed.* **2000**, 39, 1433–1436.
- 86 B. MAYR, R. TESSADRI, E. POST, M. R. BUCHMEISER, *Anal. Chem.* **2001**, 73, 4071–4078.
- 87 S. LUBBAD, B. MAYR, C. G. HUBER, M. R. BUCHMEISER, *J. Chromatogr. A* **2002**, 959, 121–129.
- 88 S. LUBBAD, M. R. BUCHMEISER, *Macromol. Rapid Commun.* **2002**, 23, 617–621.
- 89 M. R. BUCHMEISER, *Macromol. Rapid Commun.* **2001**, 22, 1081–1094.
- 90 M. R. BUCHMEISER, *J. Molec. Catal. A: Chemical* **2002**, 190, 145–158.
- 91 *Monolithic Separation Media* (Eds: F. SVEC, Z. DEYL), Elsevier, Amsterdam, **2002**.
- 92 M. MAYR, B. MAYR, M. R. BUCHMEISER, *Angew. Chem.* **2001**, 113, 3957–3960; *Angew. Chem. Int. Ed.* **2001**, 40, 3839–3842.
- 93 M. R. BUCHMEISER, F. SINNER, PCT 409 095 (A 960/99, 310599), PCT/EP00/04 768, WO 00/73782 A1, EP 00929552.8
- 94 G. ERTL, H. KNÖZINGER, J. WEITKAMP, In: *Preparation of Solid Catalysts*, Wiley-VCH, Weinheim, **1999**.
- 95 E. C. PETERS, F. SVEC, J. M. J. FRÉCHET, *Adv. Mater.* **1999**, 11, 1169–1181.
- 96 M. R. BUCHMEISER, *Angew. Chem.* **2001**, 113, 3911–3913; *Angew. Chem. Int. Ed.* **2001**, 40, 3795–3797.
- 97 A. E. RODRIGUES, *J. Chromatogr. B* **1997**, 699, 47–61.
- 98 Y. XU, A. I. LIAPIS, *J. Chromatogr. A* **1996**, 724, 13–25.
- 99 D. SYKORA, F. SVEC, J. M. J. FRÉCHET, *J. Chromatogr. A* **1999**, 852, 297–304.
- 100 C. VIKLUND, F. SVEC, J. M. J. FRÉCHET, K. IRGUM, *Chem. Mater.* **1996**, 8, 744–750.
- 101 C. VIKLUND, E. PONTÉN, B. GLAD, K. IRGUM, P. HÖRSTEDT, F. SVEC, *Chem. Mater.* **1997**, 9, 463–471.
- 102 Q. C. WANG, F. SVEC, J. M. J. FRÉCHET, *Anal. Chem.* **1993**, 65, 2243–2248.
- 103 T. B. TENNIKOVA, Z. DEYL, F. SVEC, Elsevier, Amsterdam, **2001**.
- 104 C. A. LEON Y LEON, M. A. THOMAS, *GIT Lab. J.* **1997**, 2, 101–104.
- 105 M. SZWARC, *Makromol. Chem. Rapid Commun.* **1992**, 13, 141–145.
- 106 S. PENCZEK, P. KUBISA, R. SZYMANSKI, *Makromol. Chem. Rapid Commun.* **1991**, 12, 77–80.
- 107 A. F. JOHNSON, M. A. MOHSIN, Z. G. MESZENA, P. GRAVES-MORRIS, *J. M. S.-Rev. Macromol. Chem. Phys.* **1999**, C39, 527–560.
- 108 M. SZWARC, *J. Polym. Sci. A Polym. Chem.* **1998**, 36, ix–xv.
- 109 O. W. WEBSTER, *Science* **1991**, 251, 887–892.
- 110 M. P. NANDAKUMAR, E. PÅLSSON, P.-E. GUSTAVSSON, P.-O. LARSSON, B. MATTIASSON, *Bioseparation* **2001**, 9, 193–202.
- 111 M. SCHOLL, S. DING, C. W. LEE, R. H. GRUBBS, *Org. Lett.* **1999**, 1, 953–956.
- 112 M. SCHOLL, T. M. TRNKA, J. P. MORGAN, R. H. GRUBBS, *Tetrahedron Lett.* **1999**, 40, 2247–2250.
- 113 M. R. BUCHMEISER, M. MAYR, B. MAYR, Austrian Pat. Appl. A219/2001, 409 095
- 114 M. R. BUCHMEISER, O. NUYKEN, J. KRAUSE, Austrian Patent Application, patents pending **2002**.
- 115 M. MAYR, B. MAYR, M. R. BUCHMEISER, *Designed Monomers and Polymers* **2002**, 5, 325–338.
- 116 S. C. SCHÜRER, S. GESSLER, N. BUSCHMANN, S. BLECHERT, *Angew. Chem.* **2000**, 112, 4062–4065; *Angew. Chem. Int. Ed.* **2000**, 39, 3898–3901.
- 117 M. R. BUCHMEISER, *Chem. Rev.* **2000**, 100, 1565–1604.
- 118 J. KRAUSE, O. NUYKEN, M. R. BUCHMEISER, submitted **2003**.
- 119 B. MAYR, G. HÖZL, K. EDER, M. R. BUCHMEISER, C. G. HUBER, *Anal. Chem.* **2002**, 74, 6080–6087.

3.8

Telechelic Polymers from Olefin Metathesis Methodologies

Christopher W. Bielawski and Marc A. Hillmyer

3.8.1

Introduction and Background

Polymers that bear reactive groups at their chain termini are commonly referred to as telechelic polymers (Figure 3.8-1). They are often low- to moderate-molecular-weight materials used as precursors in the synthesis of more architecturally complex macromolecules. For example, block copolymers, multi-armed copolymers with comb-, ladder-, or star-shaped structures, cyclic polymers, polymeric networks, and polymers of ultra-high molecular weight have all been prepared using telechelic polymers [1]. Thus, since they directly influence size, shape, and composition of the final macromolecular material, the controlled synthesis of telechelic polymers remains an important objective in modern polymer chemistry.

Although telechelic polymers have been described in the literature for many decades, a universally adopted nomenclature of these macromolecules has not yet been realized. Regardless, classification of telechelic polymers is generally based on the type and number of end groups. For example, a symmetrically end-functionalized linear macromolecule (whose chain termini are composed of identical functionality) is formally a ditelechelic polymer; however, the abbreviated term “telechelic polymer” is more commonly employed. Similarly, polymers with multiple functionalized chain ends are classified by the number of their end groups (for example, three- and four-armed polymers would be termed tri- and tetratelechelic, respectively). Polymeric materials with only one functional end group may be described as semi- or monotelechelic; however, reference to the single functionalized end group is preferred, and we suggest that “telechelic” should be reserved for difunctional materials. Finally, linear analogues with differentially functionalized chain ends are termed heterotelechelic. For clarity and conciseness, we will generally limit our discussion of telechelic polymers to linear polymers in which both of the chain ends are identical.

Telechelic polymers have been employed in a variety of industrial-scale applications. The oldest and most important use is in the synthesis of polyurethanes. In general, hydroxy end-functionalized telechelic polymers and di- or triisocyanates react to form the corresponding urethane-based segmented block copolymers or

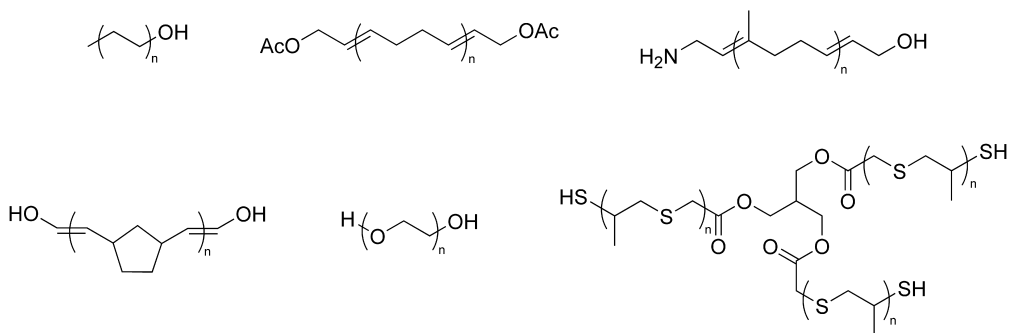


Fig. 3.8-1. Various telechelic and end-functionalized polymers.

cross-linked networks [2]. The diverse supply of hydroxy end-functionalized telechelic polymers and isocyanates currently available has led to libraries of polyurethanes with a wide range of physical properties. As such, many of the more than 5 million tons of polyurethane-based products manufactured every year employ various forms of telechelic polymers [3]. Furthermore, due to their low molecular weight and low glass transition temperatures (T_g), telechelic polymers often have very low viscosities and therefore are ideal components in reaction injection molding (RIM) applications [4].

Telechelic polymers have also been used as starting materials for the synthesis of ABA triblock copolymers with a “soft” (low T_g) midblock and “hard” (high T_g or semi-crystalline) end segments. These so-called thermoplastic elastomers behave as typical cross-linked rubbers at temperatures below the T_g of the hard segments, but they can be melted (softened) and processed at high temperatures [5]. As such, mixtures of telechelic polymers whose end groups display complementary reactivity (for example, hydroxy and carboxylic acid end-functionalized telechelic polymers) can be combined to form AB multiblock (segmented) block copolymers. Also, block copolymers can be prepared from telechelics by initiating a new polymerization from one or both of its chain ends. Thus, the preparation of block copolymers from telechelic polymers requires precise synthetic techniques that lead to well-defined end groups.

The synthesis of structurally complex polymeric materials has also relied on telechelic polymers. For example, in addition to providing a convenient handle for initiating a new polymerization or for the precise attachment of other preformed polymers, the end groups may be linked together to form polymeric networks. The end groups also may be used for attaching or grafting polymers to a surface in a specific fashion rather than relying on non-specific adsorption. More recently, attention has been directed toward preparing telechelic polymers whose end groups are capable of non-covalently associating with each other and thus may function as thermoplastic elastomers [6, 7].

As the number of applications for telechelic polymers increases, the demand for such materials with an even wider range of properties will continue to grow.

However, while recent advances in catalysis and other polymerization methods has steadily advanced, the ability to selectively place functional groups on the ends of polymer chains remains challenging. In many cases, both classical stepwise condensation polymerizations and radical polymerization techniques are commonly used.

Telechelic polymers are the default reaction products of typical step polymerizations. However, the use of radical polymerizations requires appropriately functionalized initiators so that a functional group can selectively be placed at one end of a polymer chain. A telechelic polymer is later formed by either transforming the active species through an end-capping reaction (telomerization) or by termination with a coupling reaction. Unfortunately, undesirable chain-transfer and terminating side reactions occur in typical radical polymerizations and lead to polymer chains with end functionalities that are either greater or less than two. This has adverse effects when using these polymers in subsequent chain-extension or cross-linking reactions. Furthermore, the synthesis of low-molecular-weight polymers can be challenging, and broad molecular weight distributions and branched polymer chains are often observed. Many of these drawbacks have been overcome recently with the development of controlled radical polymerizations such as atom transfer radical polymerization (ATRP), which provides a means of effectively “controlling” the radical polymerization by minimizing the concentration of free radicals. However, post-polymerization modifications are still necessary to install functional groups on the chain ends, and non-quantitative functionalization frequently is observed [8].

Thus, it remains desirable to synthesize end-functionalized polymers with precisely controlled structures, tunable molecular weights, narrow molecular weight distributions, and high degrees of end-functionalization. Toward this end, living polymerizations are commonly employed since they are (under ideal conditions) free of chain termination and chain transfer, which enables the generation of monodispersed polymers of predictable molecular weight. Furthermore, their propagating chain ends are highly reactive and can readily be transformed into a variety of functional groups through further reaction. Although a variety of living polymerization techniques exist, the most commonly employed system for preparing telechelic polymers is the anionic polymerization of styrenes, 1,3-butadienes, and isoprenes [9]. Similarly, living cationic polymerization has been used for the synthesis of telechelic vinyl ethers, styrenes, and isobutylenes [10]. Unfortunately, such ionic polymerizations mandate scrupulously clean conditions. Even small quantities of impurities can result in depressed degrees of end group functionalization. Finally, appropriately functionalized initiators and terminating agents must be used that, due to the polymerization's inherently low functional group tolerance, may require additional protection/deprotection steps [11].

Ring-opening polymerization is another commonly employed technique for synthesizing telechelic polymers. In fact, various polyether polyols, one of the main components in the synthesis of polyurethanes described above, are prepared on an industrial scale using this method. Generally, cyclic ethers such as ethylene oxide or ϵ -caprolactone are opened using various metal, acidic, or basic species, and

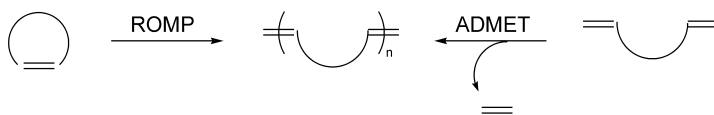


Fig. 3.8-2. Schematic of ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) polymerization.

their respective polymerizations often proceed through an ionic-type mechanism. As in other radical- and ionic-based methods, functionalized initiators, terminating agents, and transfer agents must be used. Additionally, the nature of propagating species such as metal alkoxides limits synthesis to mostly hydroxy-terminated polymers. Thus, post-polymerization modification steps become necessary if other functional groups are desired.

Herein, we will review the use of various metathesis polymerization techniques for the synthesis of telechelic polymers. Both ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) polymerization can be utilized for the preparation of telechelic polymers (Figure 3.8-2). In particular, ROMP has emerged as a highly useful technique for preparing an extremely wide array of unsaturated polymers. The library of monomers that can be polymerized using ROMP is quite large and allows extensive tailoring of the resultant physical properties of the polymer product. The technique uses cyclic olefins and, like the ring-opening polymerizations described above, is enthalpically driven by the release of ring strain. However, in ROMP extensive chain transfer to polymer may occur and the polymerization is often under thermodynamic control. This is also the case in ADMET polymerizations. As will be described below, distinct advantages for the synthesis of telechelic polymers can be realized using either of these techniques. Furthermore, the recent developments in olefin metathesis have produced highly functional-group-tolerant catalysts, allowing the polymerizations to be performed under extremely mild and user-friendly conditions. Such features make ROMP and ADMET attractive synthetic alternatives for preparing telechelic polymers.

3.8.2

Telechelic Polymers from Metathesis Polymerizations

Acyclic monofunctional olefins may be included as chain-transfer agents (CTAs) to help regulate the molecular weight of polymers produced during a ROMP [12]. However, when α,γ -difunctional olefins are employed as CTAs, difunctional telechelic polymers can be prepared. In the chain-transfer reaction with a symmetric α,γ -difunctional olefin, a propagating polymer chain is terminated with a functional group and forms a new substituted metal alkylidene. This complex subsequently reacts with monomer or a preformed polymer chain and effectively transfers the active species from one chain to another (Figure 3.8-3). The process preserves the number of active catalyst centers and leads to symmetric telechelic polymers with a

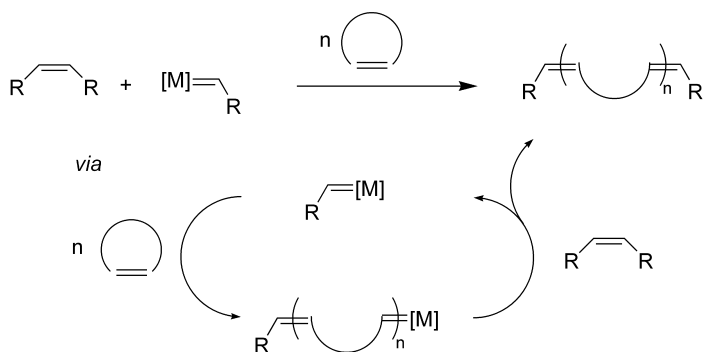


Fig. 3.8-3. Generic mechanism of generating telechelic polymers using ROMP/CT.

number average functionality (F_n), or average number of functional groups per polymer chain, that approaches 2.0.

The mechanism that operates in a ROMP is directly related to other metathesis-based polymerizations/depolymerizations performed in the presence of a chain-transfer agent. All processes require the transfer of a functionalized moiety from the “functionalized” catalyst center to a polymer chain and a reaction of the “propagating” catalytic species with the chain-transfer agent to regenerate the “functionalized” catalyst. Concomitant with chain transfer, monomer addition or condensation can also occur during ROMP or ADMET polymerizations, respectively. In metathesis degradation processes, intermolecular chain transfer between polymer chains occurs on the same timescale as the incorporation of the monomer or chain-transfer agent. In fact, since all of the metathesis-driven processes for the preparation of telechelic polymers are related, one can generate a general set of requirements for the successful generation of telechelic polymers with controlled molecular weights and high functionality.

Under ideal conditions, polymers with precisely controlled molecular weights and F_n values equal to exactly 2.0 would be obtained. High catalytic activity and tolerance are arguably the most important features of any metathesis-based system for the preparation of telechelic polymers. Premature catalyst deactivation has two detrimental consequences. First, the polymerization may not be complete before the catalyst becomes inactive, and thus both unreacted monomer and chain-transfer agent will remain, necessitating the need for subsequent purification. Secondly, if the decomposition of the catalyst leads to the generation of non-functional (or undesirable) polymer end groups, the average functionality of the material will be compromised. Furthermore, the more catalyst used in a given system, the more the initiating fragment from the catalyst will contribute to the polymer end groups. In the absence of fortuitous termination reactions, the only polymer end groups that do not contain residues from the chain-transfer agent are those from the initiating alkylidene and the end-capping reagent (end groups from termination processes). In principle, these end groups could be chosen to match those on the chain-transfer agent. If the catalyst does not decompose over

the course of the reaction in a ROMP-chain transfer (ROMP/CT) system, then the molecular weight of the product polymers can be readily described as an equilibrium process.

3.8.2.1

Molecular Weight and Functionality Control in a ROMP/CT System

In most reports that describe molecular weight regulation of polymers produced via ROMP, acyclic olefins are included, which ultimately reduces the molecular weight of the polymer. Here a relationship between number average degree of polymerization, X_n , and the concentration of chain-transfer agent is derived for an equilibrium-controlled ROMP/CT system. The number average degree of polymerization, X_n , is defined as the average number of structural (monomer) units per polymer chain [13]. For a ROMP system in the absence of intramolecular chain transfer (i.e., backbiting reactions) and with quantitative catalyst (C) initiation, the total number of polymer chains is equal to $[C]_0$. At time t , X_n is given by

$$X_n = \frac{[M]_0 - [M]_t}{[C]_0} \quad (1)$$

where the subscripts 0 and t denote initial concentration and concentration at time t , respectively, and M denotes monomer. This is related to the expression for a typical living polymerization [9]. Even in a polymerization where intermolecular chain transfer to polymer is occurring, Eq. (1) should still hold since the total number of chains is preserved. In this case, the polydispersity index of the polymers should approach 2.0 (which statistically is the most probable distribution) [13]. Since an initiator is required to form polymer, the total number of linear chains should always be equal to the number of catalyst molecules. Any termination process would only decrease the total number of active chains. Chain-transfer reactions other than chain transfer to polymer (e.g., chain transfer to monomer, to CTA, or to solvent) would increase the number of chains in the system. However, there are typically no viable mechanisms for chain transfer of a propagating species to monomer or to solvent in a typical ROMP.

However, there are two possible chain-transfer reactions that can occur in the ideal system. The first type of reaction, chain transfer to polymer, can occur in an intra- or intermolecular fashion. Intermolecular chain transfer to polymer is the reaction of a growing polymer chain with another chain in the system. As a result, the propagating species is transferred from one polymer chain to another, but there is no change in the total number of polymer chains (see above). Intramolecular chain transfer to polymer is classified as a backbiting reaction. Reaction of a propagating species with a double bond in its own polymeric backbone would result in the formation of cyclic oligomers. Again, there is no change in the total number of linear polymer chains, and any cyclic oligomer (including the monomer) in the reaction can be treated as unreacted monomer ($[M]_t$). Thus, to minimize the concentration of cyclic oligomers, polymerizations should be performed

at conditions that minimize the relative equilibrium monomer concentration (typically high $[M]_0$ and low temperatures for exothermic polymerizations).

The second type of chain transfer is the desired reaction of chain transfer to acyclic olefin. For every chain-transfer reaction to an acyclic olefin, the total number of linear polymer chains will increase by one provided that the new catalytic species can continue to add more monomer. Thus, the total number of polymer chains is equal to the total number of initial catalytic species ($[C]_0$) plus the total number of chains produced by a chain-transfer event ($[CTA]_0 - [CTA]_t$). Therefore, in a typical ROMP/CT system, the X_n can be defined as

$$X_n = \frac{[M]_0 - [M]_t}{([CTA]_0 - [CTA]_t) + ([C]_0 - [C]_t)} \quad (2)$$

If the catalyst concentration is chosen such that $[CTA]_0 \gg [C]_0$, then in the limit of complete conversion of both the M and the CTA, Eq. (2) reduces to

$$X_n = \frac{[M]_0}{[CTA]_0} \quad (3)$$

In an ideal ROMP/CT system, there is no termination of the active species, the catalyst concentration is much greater than the concentration of CTA, the monomer is completely converted to polymer, and all of the CTA is incorporated into polymer chains. If these conditions are met, Eq. (3) should be valid. The expression for X_n given in Eq. (3) is similar to the polymerization of an epoxide initiated by a metal alkoxide or hydroxide in the presence of protic substances such as alcohols [13].

The number average functionality F_n of a telechelic polymer is defined as the number of functional groups per polymer chain. In the synthesis of telechelic polymers by ROMP/CT, the number of functional end groups that are incorporated into a polymer chain is ideally equal to twice the number of added chain-transfer agents, since each chain-transfer agent contains two functional groups. The total number of polymer chains is equal to the total number of initiators as defined above. The only chain ends that do not contain a fragment from the chain-transfer agent are those from the initial catalyst and/or from any termination reaction. An expression for the theoretical functionality of a polymer in a ROMP/CT system is given in Eq. (4).

$$F_n = \frac{2([CTA]_0 - [CTA]_t)}{([CTA]_0 - [CTA]_t) + ([C]_0 - [C]_t)} \quad (4)$$

In the limit of 100% conversion of the chain-transfer agent and complete initiation of the catalyst, Eq. (4) reduces to:

$$F_n = \frac{2[CTA]_0}{[CTA]_0 + [C]_0} \quad (5)$$

It is convenient to define r as the ratio of $[\text{CTA}]_0$ to $[\text{C}]_0$. This ratio is related to the number of functionalized end groups to non-functionalized end groups, where the latter is any group that does not come from the CTA. The F_n as a function of r is given in Eq. (6).

$$F_n = \frac{2r}{r + 1} \quad (6)$$

For functionalities that are very close to 2, an r value of at least 100 must be used (i.e., $F_n = 200/101 = 1.98$). Again, this is in the limit of quantitative conversion of the CTA.

As the target molecular weight of a telechelic polymer (from the preceding section, $X_n \approx [\text{M}]_0/[\text{CTA}]_0$) becomes larger, the negative contribution to F_n by the catalyst becomes even more severe. That is, r becomes smaller if the $[\text{M}]_0/[\text{C}]_0$ ratio remains constant and the concentration of the chain-transfer agent is decreased. This is usually the case when higher-molecular-weight telechelic polymers are desired. In order to achieve F_n values that are very close to 2.0, r values greater than 100 must be used (which leads to a $F_n > 1.98$). This necessitates adjustment of the $[\text{M}]_0/[\text{C}]_0$ ratio at different $[\text{M}]_0/[\text{CTA}]_0$ ratios. For example, if the target X_n is 10 and the desired functionality is >1.98 , then the $[\text{M}]_0/[\text{CTA}]_0$ ratio should be ≈ 10 and r should be >100 . This leads to a $[\text{M}]_0/[\text{C}]_0$ ratio of 1000 (at $r = 100$). Simply, the more catalyst in the system relative to the CTA, the more undesirable end groups (i.e., from the catalyst fragments) will be realized. Development of catalysts that deliver functionalized fragments during the initiation process or catalysts with extraordinary activity to permit extremely low catalyst loadings are critically important to alleviate this problem.

There are no viable mechanisms in this type of ROMP/CT system that would result in F_n values greater than 2.0. However, there are two possibilities in a ROMP/CT system that would reduce the F_n . The first is the contribution of the initiating carbene and the end group derived from any termination process (see above). The second is the formation of cyclic oligomers, since they will contribute to the total number of “chains” but do not have any end groups. Therefore, formation of cyclic oligomers will negatively affect the average functionality (F_n). Low-molecular-weight cyclics are typically removed from the polymer by precipitation in an appropriate non-solvent for the linear (i.e., telechelic) polymer [14].

In principle, the above analysis can also be applied to ADMET polymerization and metathesis degradation routes to telechelic polymers. One simply needs to account for the number of polymer chains and end groups in the specific system of interest. While the nature of the chain-transfer agent and the monomeric or polymeric substrate is important to consider in any metathesis-based system for the synthesis of telechelic polymers, the composition, activity, and tolerance of the catalyst are of critical importance. This chapter addresses the synthesis of telechelic polymers first by examining seminal work using first-generation, ill-defined metathesis catalysts. While there have been several useful advances based on these sys-

tems, the ability to systematically modulate the activity of the catalyst, to define the structure of the initiating alkylidene, and/or to control the mode of termination in these multi-component catalysts is very limited. Furthermore, this often resulted in irreproducible activities from batch to batch. In addition, the Lewis acid co-catalysts typically found in these systems often reacted with functional groups on the chain-transfer agent or with the monomer itself and led to unwanted byproducts and catalyst deactivation. These problems were eventually overcome by the development and use of well-defined, Lewis-acid-free metal-alkylidene complexes. Furthermore, this later class of catalysts could produce polymer chains that remained active in the absence of an end-capping reagent. The latest generations of metathesis catalysts have certainly brought significant advances to the field of telechelic polymer synthesis and are reviewed in the subsequent sections.

3.8.3

Syntheses and Applications of Telechelic Polymers Prepared Using Metathesis

Early methodologies producing telechelic polymers via metathetical routes involved the use of cyclic olefins in conjunction with acyclic olefins that effectively functioned as chain-transfer agents. While molecular weight control was the desired outcome, the placement of functional groups (originating from either the catalyst or the included chain-transfer agent) at the ends of the resultant polyalkenamers was a consequence with potential utility. The main problem that thwarted initial efforts was the intolerance of “classical” catalysts to the target functionality. Starting in the late 1980s, well-defined metathesis catalysts were developed and these efforts ultimately led to the discovery of discrete organometallic complexes that were effective metathesis catalysts and, importantly, were tolerant of functionality. As a result the synthesis of telechelic polymers using metathesis resurfaced in the 1990s as a particularly efficient methodology. Those advances continue today and build on the important work that came in the early days of chain transfer in metathesis polymerizations. Since telechelic polymers are defined as polymers with reactive end groups, our review on the preparation of telechelic polyalkenamers will be limited to polymers containing end groups such as esters, alcohols, and halogens. Telechelic polyalkenamers with alkyl or vinyl end groups will be excluded [15]. The reader is referred to the numerous references regarding efforts at controlling molecular weight by adding non-functional olefins such as terminal or internal alkenes (e.g., 1-hexene, 3-hexene, and 4-octene) [16–19]. Furthermore, since by definition telechelic polymers have exactly two functional end groups, particular attention will be devoted toward evaluating the extent to which the polymer end groups are actually functionalized. As stated earlier, this is usually expressed as the number average functionality (F_n) and is defined as the average number of functional groups per polymer chain. Attention will also be directed toward examining molecular weight control and polydispersity, since these provide mechanistic insight.

3.8.3.1

Synthesis of Telechelic Polymers Using Ill-Defined Catalysts

Early efforts at preparing telechelic polymers using acyclic functionalized alkenes and various cycloalkenes were designed to give difunctional polymeric precursors for polycondensation reactions [20, 21]. Starting with reports appearing in 1980, the ring-opening cross-metathesis of cyclooctadiene [22, 23], cyclooctene [24], or cyclopentene [25] with dimethyl 3-hexenedioate or ethyl-3-pentenoate afforded mixtures of dimethylcarboxylate end-functionalized polyalkenamers (Figure 3.8-4). Typically, the reactions were catalyzed by the $\text{WCl}_6/\text{SnMe}_4$ catalyst system at temperatures up to 100 °C. Although isolated yields were generally not reported, the major products appeared to be the ring-opened monomer and dimer (i.e., $X_n = 1$ or 2). Furthermore, catalyst stability and activity were limited in the presence of the ester group on the chain-transfer agent. However, Otton noted that catalyst activity could be improved by increasing the number of carbon atoms between the double bond and the functional group on the chain-transfer agent [24]. Initial investigations by Reyx at preparing chloro end-functionalized telechelic polybutadienes employed 1,4-dichloro-2-butene as the chain-transfer agents; however, no product was obtained. Since W/Al mixtures are strongly Lewis acidic, the catalyst was believed to activate the allyl chloride moiety and lead to various (cationic-based) detrimental side reactions. However, by extending the chloro group further away from the olefin, chloro-terminated telechelic polybutadienes were later obtained [26]. A similar approach to ester-terminated polybutadienes through the metathesis degradation of polybutadiene in the presence of ester-functionalized terminal olefins was reported [27]. However, as seen with the other approaches, catalyst stability appeared to limit degradation and mixtures of products were obtained. The F_n of the polymers was not reported in any of these cases, but for the oligomeric examples, it appeared to be close to 2.0.

These reports focused on using cyclic olefins with a relatively low degree of ring strain. As noted above, this led mainly to low-molecular-weight telechelic polymers containing only a few monomer units. Thus, attention shifted toward using highly strained monomers such as norbornene and dicyclopentadiene in hopes that their higher rates of polymerization would result in higher-molecular-weight materials. End-functionalized polynorbornenes were first reported by Fontanille in 1991 [28]. Indeed, the higher polymerization rates turned out to be advantageous, as relatively high-molecular-weight ester-terminated telechelic polynorbornenes were

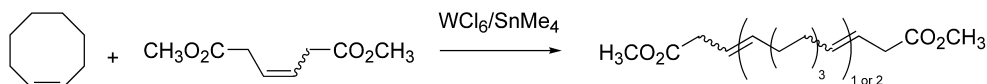


Fig. 3.8-4. Synthesis of end-functionalized polyoctenamers using a difunctional chain-transfer agent and a classical metathesis catalyst system. Pinazzi, C. P.; Campistron, I.; Croissandeau, M. C.; Reyx, D. J. *Mol. Cat.* **1980**, *8*, 325.

obtained when norbornene was polymerized in the presence of a variety of ester-containing chain-transfer agents. This was further seen in the relatively high chain-transfer agent-to-norbornene ratios that were required (up to 2:1). Regardless, positive linear correlation with the M_n of the isolated telechelic polymer was observed and suggested that some control over molecular weight was achievable. The high chain-transfer agent-to-monomer ratio may also be the cause of the polydispersities (PDIs > 2.5), which were higher than expected for an equilibrium-controlled reaction (PDI = 2.0). A comprehensive study later revealed that the reaction was governed by the relative rates of chain transfer and polymerization [29]. The F_n of the polymers was found in a range between 1.7 and 1.9. Subsequent saponification or reduction of the ester groups afforded acid- and hydroxy-terminated telechelic polynorbornenes, respectively.

This approach was later extended to the synthesis of ester and hydroxy end-functionalized dicyclopentadiene [30]. However, use of the catalyst $WCl_6/SnMe_4$, which was successful for norbornene, led to insoluble cross-linked networks when applied to dicyclopentadiene. Thus, attention shifted toward using the less-active $W(OAr)_2Cl_4/SnMe_4$ catalyst system. Although small amounts of cross-linked material were still obtained, they were easily removed by filtration. By using hex-3-ene-1,6-dimethyldioate as the chain-transfer agent, difunctional oligomers with molecular weights that were dependent on the initial concentration of chain-transfer agent were obtained. When using NMR spectroscopy, the F_n values were found to range between 1.7 and 2.0 for oligomers with M_n values near 2000 g mol^{-1} . Quantitative reduction of ester end groups afforded hydroxyl end-functionalized oligomers. Such polymers are expected to complement the polybutadiene and polynorbornene hydroxy end-functionalized telechelic polymers in polyurethane-based applications (Figure 3.8-5).

Almost at the same time, Chung and Chasmawala reported a degradative approach to hydroxy end-functionalized telechelic polybutadienes [31, 32]. Capitalizing on the fact that olefin metathesis is a fast and reversible reaction, they degraded a high-molecular-weight polymer in the presence of an internal olefin to form a relatively low-molecular-weight telechelic polymer (Figure 3.8-6). *cis*-1,4-Polybutadiene was degraded in the presence of 1-hexenyl-6-(9-BBN) (9-BBN: 9-borabicyclononane) and $WCl_6/SnMe_4$. The depolymerization was performed under a mild vacuum to remove the ethylene byproduct. As expected, the viscosity of the solution decreased as the reaction progressed, and the molecular weight was successfully reduced from 172 kg mol^{-1} to 1 kg mol^{-1} in less than 30 minutes. Inter-

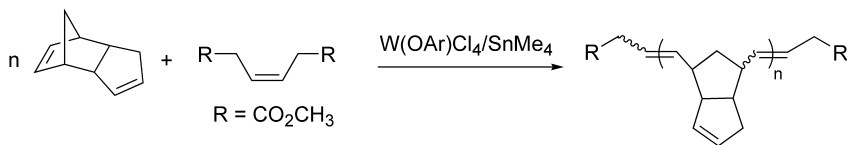


Fig. 3.8-5. Synthesis of telechelic polydicyclopentadienes using a $W(OAr)_2Cl_4/SnMe_4$ catalyst system. Heroguez, V.; Soum, A.; Fontanille, M. *Polymer* **1992**, 33, 3302.

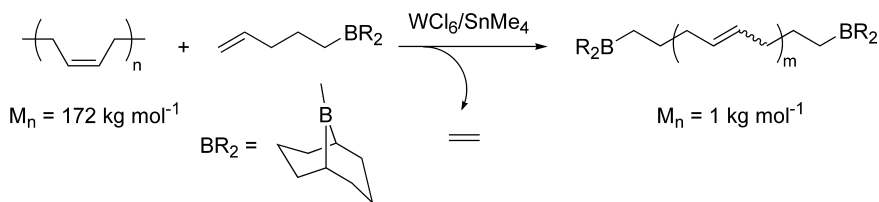


Fig. 3.8-6. Metathesis degradation route to borane end-functionalized telechelic polybutadienes. Chung, T. C.; Chasmawala, M. *Macromolecules* **1991**, *24*, 3718.

estingly, the polydispersity changed from 2.5 to 1.9, which is near the expected value for a thermodynamically controlled process [13]. After an oxidative workup, hydroxy end-functionalized polymers were obtained in good yield. While not all chains were perfectly difunctionalized, polymers with F_n values near 2.0 were obtained after purification using chromatographic methods. The success in preparing telechelic polymers via this approach was attributed to the stability of borane groups to the metathesis catalyst [33, 34].

The borane approach was later expanded to using cyclooctadiene instead of polybutadiene as the butadiene equivalent [35]. In an approach similar to that described above, cyclooctadiene was combined with the symmetrical difunctional chain-transfer agent 1,10-bis(9-BBN)-5-decene, and the ROMP/CT process was mediated by the $\text{WCl}_6/\text{SnMe}_4$ catalyst system. Since the catalyst itself is a probable source of ill-defined functionality, relatively high monomer:catalyst ratios of 500:1 were used. By varying the monomer:chain-transfer agent ratio from 10:1 to 100:1, telechelic polymers with molecular weights ranging from 7 to 51 kg mol^{-1} were obtained. Although the molecular weights were higher than their theoretical value, a linear correlation with the monomer-to-chain-transfer agent ratio was observed. In all cases, the polydispersity index values were near 2.0 and yields were typically 70%. Subjecting the telechelic polymers to either $\text{H}_2\text{O}_2/\text{NaOH}$ or ICl/NaOAc afforded hydroxy and iodo end-functionalized telechelic polybutadienes, respectively.

Chung later applied this approach to the synthesis of telechelic polyisobutylenes through the metathetical degradation of polyisobutylene-co-butadiene copolymers [36]. Unfortunately, mixtures of polymers with mono- and difunctional end groups were obtained, which may be a result of competitive reaction with the 1,2-butadiene regioisomers in the polymer backbone ($\sim 10\%$) and the methyldiene units from the catalyst. After chromatographic separation, approximately 20% of the polymer chains were difunctionalized telechelic polymers. The alkylborane end groups were quantitatively converted into hydroxy and iodo groups as described above. The hydroxy end-functionalized polymers were successfully used as macro-initiators for the synthesis of polycaprolactone-*b*-polyisobutylene block copolymers.

A two-step olefin metathesis process was reported by Nubel to prepare ester-functionalized telechelic polybutadienes [37]. In the first step of this process,

methyl undecyclenate was dimerized using $\text{WCl}_6/\text{SnMe}_4$ to afford dimethyl 10-eicosene-1,20-dioate diester as the chain-transfer agent plus ethylene. The second step employed $\text{WCl}_6/\text{SnMe}_4$ to mediate the ROMP of cyclooctadiene in the presence of the chain-transfer agent. Polybutadiene with an exclusive 1,4-microstructure was isolated in yields of up to 80% and was determined by extensive NMR analysis to have an F_n near 2.0. However, highly pure cyclooctadiene (>99.9%) and very low catalyst loadings were necessary to achieve this result. Cyclooctadiene typically is contaminated with 4-vinylcyclohexene, and this contaminant can function as a (non-functional) chain-transfer agent and depress the F_n . Regardless, the telechelic polymers were used in a subsequent chain-extension reaction with 1,6-hexanediol to afford high-molecular-weight polyesters. The use of 1,5,9-cyclododecatriene in lieu of cyclooctadiene also afforded the respective telechelic polymers in the presence of the chain-transfer agent. Since 1,5,9-cyclododecatriene does not contain 4-vinylcyclohexene as an impurity, elaborate purification was not required for this monomer. However, approximately 1% of the end groups were terminal olefins and probably reflect the monomer:catalyst ratio (340:1) employed during this reaction.

A noted above, a major drawback to the ill-defined catalysts is that they are typically highly Lewis acidic and often lead to acid-catalyzed side reactions such bond isomerization or halide activation. Ichikawa and Fukuzumi reported a highly selective metathesis catalyst that consisted of WCl_6 , $\text{Sn}(\text{alkyl})_4$, and various alkyl acetates [38]. The alkyl acetate was believed to function as a weak Lewis base that effectively neutralized the Lewis acidity of the metathesis catalyst. Nubel recalled this discovery and applied it toward the synthesis of telechelic polymers [39]. Acyclic diene metathesis polymerization of 1,5-hexadiene using the modified catalyst ($\text{WCl}_6/\text{SnMe}_4/\text{PrOAc}$) was conducted in the presence of 5-acetoxy-1-pentene as the chain-transfer agent. Although acetoxy end groups were observed in the isolated polymer, a minor (~20%) amount of vinyl end groups was observed as well. However, no double-bond isomerization (or other side reactions) was observed and the resultant polybutadiene exhibited only 1,4 regioisomers.

3.8.3.2

Synthesis of Telechelic Polymers Using Well-Defined Metal Alkylidenes

As noted above, the use of ill-defined, classical catalyst systems such as $\text{WCl}_6/\text{SnMe}_4$ are highly Lewis acidic, which often leads to undesired side reactions. Furthermore, catalyst initiation and activity are difficult to evaluate and control. Combined, these drawbacks prevented the widespread use of these catalysts for the synthesis of telechelic polymers. Thus, attention shifted toward using catalysts with well-defined structures. Because no co-catalyst is added, they are inherently less Lewis acidic and thus more functional group tolerant than their ill-defined counterparts. Well-defined catalysts are also discrete species, which allows their activities and initiation characteristics to be easily evaluated and tuned. Ultimately, these features permit one not only to calculate the upper limits of the (negative) contribution of the catalyst to the telechelic polymer's functional end groups before

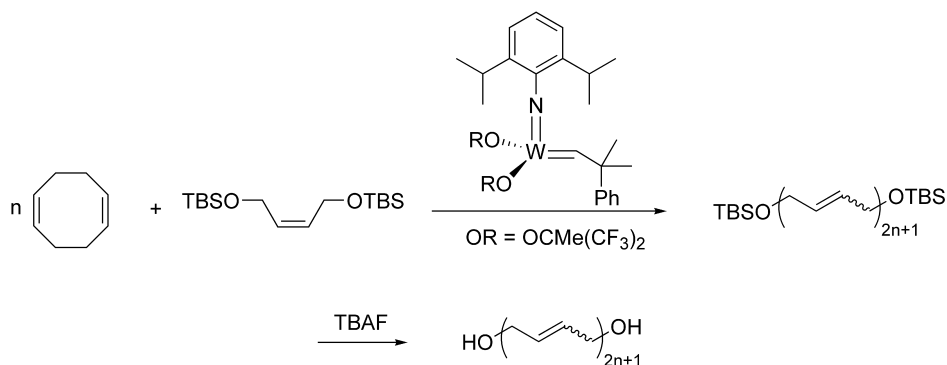


Fig. 3.8-7. Production of hydroxy end-functionalized telechelic polybutadienes using a discrete metal-alkylidene catalyst and a protected chain-transfer agent. Hillmyer, M. A.; Grubbs, R. H. *Macromolecules* **1993**, 26, 872.

the polymerization is performed but also to employ a more diverse array of functional groups.

In the first report describing the use of a discrete metal-alkylidene metathesis catalyst for the preparation of telechelic polymers, Hillmyer and Grubbs prepared a series of hydroxy end-functionalized telechelic polybutadienes [40]. In this work, cyclooctadiene was polymerized in the presence of a silyl-protected 1,4-dihydroxy-2-butene chain-transfer agent. The ROMP/CT reaction was performed in the absence of solvent, and a well-defined W complex was used as the catalyst (Figure 3.8-7). Ultimately, end-functionalized acetoxy telechelic polybutadienes were obtained with molecular weights that could be tuned by varying the initial chain-transfer agent-to-monomer ratio. However, the yield of telechelic polymer dropped off precipitously as more chain-transfer agent was employed, and this was attributed to premature catalyst decomposition. Since instability of various W complexes in the presence of allylic ethers had been previously reported [41], it was proposed that intramolecular oxygen coordination to the newly generated alkylidene (from the cross-metathesis of the W complex with the chain-transfer agent) may be attenuating catalytic activity or facilitating degradative pathways [42]. Regardless, after removing the silicon-protecting groups with tetra-*n*-butylammonium fluoride (TBAF), hydroxy end-functionalized telechelic polybutadienes were obtained with F_n values between 1.7 and 1.9. Furthermore, in all cases, the polydispersity index values for the product polymers were near 2.0, as expected.

An investigation focusing on how the chain-transfer agent and the choice of catalyst affect telechelic polymer synthesis was later reported by the same authors [43]. To enhance catalyst stability, the oxygen functionality was separated from the olefin in the chain-transfer agent by at least two methylene units. In the presence of these homologous versions of the chain-transfer agent, the W catalyst was found to be stable for over 3 months without loss in activity. Furthermore, the chain-transfer agents were also more effective in reducing/controlling molecular

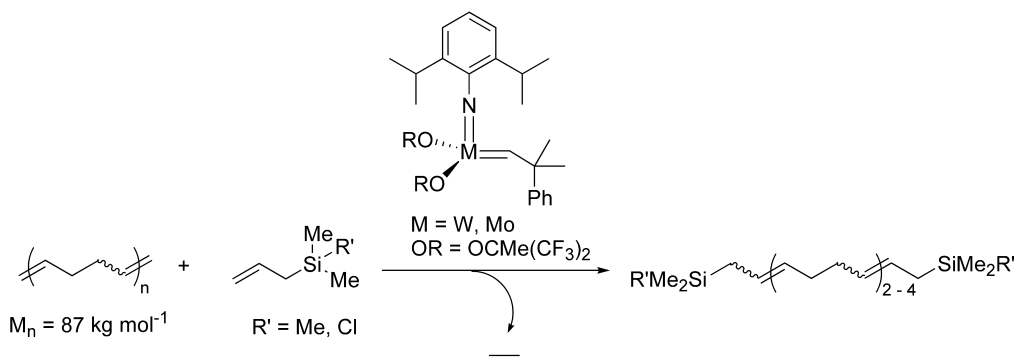


Fig. 3.8-8. ADMET polymerization route to silyl-functionalized telechelic polymers. Marmo, J. C.; Wagener, K. B. *Macromolecules* **1993**, 26, 2137.

weight and increasing polymer yield, and they afforded a nearly linear relationship between X_n and the monomer-to-chain-transfer agent ratio. However, catalyst decomposition was still occurring over the course of the polymerization when high concentrations of chain-transfer agent were employed. Thus, attention shifted toward using a well-defined metathesis catalyst based on Mo, which was known to possess an even higher degree of functional group tolerance and thermal stability when compared to its W analogue. With this catalyst, improved yields were obtained and high monomer-to-catalyst ratios (up to 2400) could be used without loss in activity. Nonetheless, either catalyst ultimately afforded an effective route to hydroxy end-functionalized telechelic polybutadienes (possessing 100% of the 1,4-regioisomer).

Early reports on using well-defined catalysts in preparing telechelic polymers also involved the ADMET depolymerization of 1,4-polybutadiene in the presence of various allyl silanes (Figure 3.8-8) [44]. For example, combining allyltrimethylsilane and commercially available polybutadiene with a well-defined W-based catalyst resulted in the immediate evolution of ethylene, stemming from the dimerization of the allylsilane. After the ethylene was removed, the reaction was diluted, and through repetitive intermolecular chain transfer between the polymer and the allyl silane dimer, low-molecular-weight oligomers with silyl end groups were obtained. Interestingly, the polybutadiene, which had an initial molecular weight of 87 kg mol^{-1} , was depolymerized to oligomers ($X_n = 2-4$) with perfect difunctionality ($F_n = 2.0$). The Mo version of the catalyst was subsequently used to synthesize allylchlorodimethyl end-functionalized telechelic polymers. The approach was subsequently used to prepare diester, disilyl ether, and diimide end-functionalized telechelic polybutadienes [45].

The mechanism yielding these telechelics is believed to proceed first through intramolecular cyclization of 1,4-polybutadiene to form cyclic oligomers. The depolymerizations were performed at concentrations below the (ring-linear chain) equilibrium concentration in order to favor the formation of low-molecular-weight

cyclic oligomers (for reference, the $[M]_c$ for cyclooctadiene expressed as C_4H_6 units is ~ 0.50 M) [46]. The cyclic oligomers then undergo metathesis with an unsaturated chain-transfer agent to form linear telechelic oligomers. Support for this claim was obtained through NMR spectroscopic analysis of the reaction mixture, which indicated that macrocyclic olefinic protons were indeed present at the early stages of the reaction. Further evidence was obtained from the fact that ADMET depolymerization was not effective under bulk conditions (i.e., performing the reaction above the ring-linear chain equilibrium concentration afforded mostly unreacted high-molecular-weight polymer). The extent of catalyst homogeneity and the viscosity of the reaction mixture were found to be additional factors that influenced the depolymerization process [47].

In a related study, the importance of furan-based materials in a variety of commercial applications prompted Wagner and coworkers to investigate the ADMET depolymerization of furan-based polymers [48]. High-molecular-weight polymers of 7-*exo*-N-methyl-7-oxabicyclo[2.2.1]hept-2,5-diene-2,3-dicarboximide, 2,3-dicarbomethoxy-7-oxabicyclo[2.2.1]hept-2,5-diene, and 2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hept-2,5-diene were first prepared using a Ru-mediated aqueous ROMP. The resultant polymers were then depolymerized using a Mo catalyst and the metathetical dimer of allyltrimethylsilane as the chain-transfer agent. The extent of depolymerization was found to depend on the functionality in the polymeric backbone. While the poly(7-oxanorbornene) derivative was found to depolymerize efficiently ($M_{n, initial} = 574$ kg mol $^{-1}$; $M_{n, final} = 2.9$ kg mol $^{-1}$), a relatively low degree of depolymerization was observed with the poly(7-oxanorboranadiene) derivative ($M_{n, initial} = 17$ kg mol $^{-1}$; $M_{n, final} = 5$ kg mol $^{-1}$). The difference may be related to intramolecular carbonyl coordination during the metathesis event in the latter polymer. The fluorinated poly(oxanorbornadiene) was also depolymerized ($M_{n, initial} = 59$ kg mol $^{-1}$; $M_{n, final} = 3$ kg mol $^{-1}$) using a similar approach. Although the F_n for these polymers was not reported, examination of the 1H NMR spectra indicated that the value was near 2.0.

The advent of well-defined Ru complexes had a major impact on the synthesis of telechelic polymers. Because of their high tolerance to a wide range of functional groups and impurities (such as oxygen and water), Ru complexes quickly became the catalysts of choice for preparing telechelic polymers. In 1995, Grubbs and coworkers reported a novel route to telechelic polymers by using polymeric precursors that contained cleavable linkages [49]. Cyclooctadiene/4,7-dihydro-1,3-dioxepin copolymers were prepared by ROMP using the Ru complexes $(Cy_3P)_2Cl_2Ru=CHR$ (Cy = cyclohexyl; Ph = phenyl; R = $CHCPh_2$ or Ph). Notably, the Ru catalyst tolerated the allylic oxygen (acetal) linkages to a much higher extent than did the W and Mo catalysts. Furthermore, acetal incorporation and polymer molecular weight were both dependent the initial monomer feed ratios. Hydroxy end-functionalized telechelic polybutadienes were subsequently obtained upon acidic workup by fragmentation of the acetal functionalities (Figure 3.8-9). Success of the acidic workup depended heavily on the type of acetal used in the reaction. For example, the benzylidene acetal could be cleaved using acidic methanol solutions, whereas the more robust methylidene required reaction with trifluoroacetic

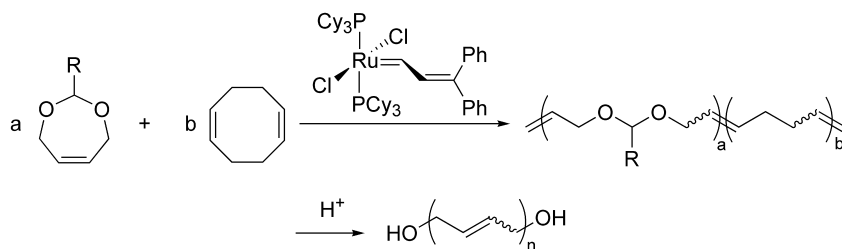


Fig. 3.8-9. Copolymerization/degradation route to telechelic polybutadienes. Fraser, C.; Hillmyer, M. A.; Gutierrez, E.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7256.

anhydride followed by a basic workup (NaOAc/MeOH). Regardless, the molecular weight of the telechelic polymers correlated with the amount of acetal in the parent copolymer. Interestingly, the polydispersities of the telechelic polybutadienes prepared from degradation of the acetal copolymers were narrower ($\text{PDI} = 1.1\text{--}1.3$) than expected for telechelics prepared through other degradative approaches ($\text{PDI} \approx 2$). Simultaneous hydrogenation and degradation of the cyclooctadiene/acetal copolymer using *p*-toluenesulfonylhydrazide was also found to be a highly efficient protocol for preparing hydroxy end-functionalized telechelic polyethylenes in one step [50].

Although each of the methods described above provides a route to telechelic polymers, each employs different monomers (or polymers) and chain-transfer agents. However, the success of the synthesis ultimately relies on the stability and activity of the catalyst employed. Thus, typically hydrocarbon monomers and protected chain-transfer agents are necessary to avoid catalyst deactivation and/or premature decomposition. As discussed above, this generally requires at least two methylene units between the functional group and the olefin in the chain-transfer agent. With the advent of well-defined and functional-group-tolerant Ru catalysts, this restriction can be circumvented [51, 52].

Grubbs and coworkers showed that the combination of cyclooctadiene with 1,4-diacetoxy-2-butene can be used to form acetoxy end-functionalized telechelic polybutadienes using the Ru catalyst $(\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHR}$ (Figure 3.8-10) [53]. The polymerizations could be performed using high monomer concentrations or even bulk monomer, and the robust nature of the catalyst allowed the use of high (5000) monomer-to-catalyst ratios. Furthermore, by varying the initial monomer:CTA ratio, the molecular weights of the resultant polymer were controlled and polymer yields were as high as 90%. In all cases, the F_n values of the polymers were near 2.0. Mechanistic investigations suggested that polymer size is initially under kinetic control and increases rapidly during the early stages of the polymerization. Subsequent backbiting/chain-transfer reactions then lead to a reduction in molecular weight, which eventually approaches its thermodynamic equilibrium (defined by the initial monomer-to-chain-transfer agent ratio). To determine whether a more direct route to hydroxy end-functionalized telechelic polybutadienes was possible,

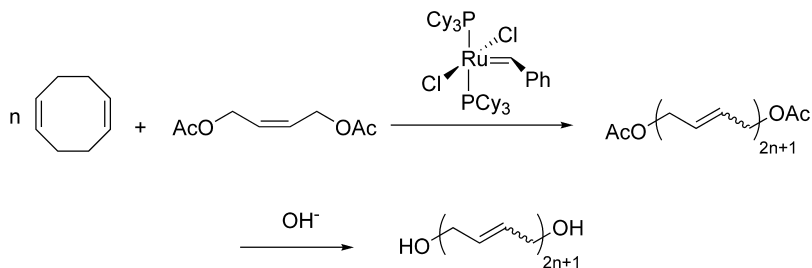


Fig. 3.8-10. Ruthenium-catalyzed protocol for the synthesis of telechelic polybutadienes using a protected chain-transfer agent. Hillmyer, M. A.; Nguyen, S. T.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 718.

1,4-dihydroxy-2-butene and its homologous analogues were investigated as potential chain-transfer agents. However, when the free alcohols were used, the polymeric products contained significant amounts of aldehyde end groups. Presumably, the Ru species that forms from the cross-metathesis of catalyst with the chain-transfer agent decomposes over the timescale of the polymerization, or the catalyst simply decomposes in the presence of the chain-transfer agent. In either case, the decomposition product, which has been previously suggested to be a ruthenium hydride species, then catalyzes the isomerization of the allyl alcohol end group to an aldehyde.

Grubbs and coworkers later expanded this approach to the preparation of chloro, 2-bromoisobutryl, carboxy, amino, epoxide, and methacrylate end-functionalized telechelic PBDs using the appropriately functionalized CTAs [54–56]. The chloro and 2-bromoisobutryl end-functionalized polymers were used as macroinitiators for the controlled radical polymerization (Cu-mediated ATRP) of styrene and methyl methacrylate to form the respective triblock copolymers (Figure 3.8-11). Selective oxidative degradation of the polybutadiene cores using $\text{OsO}_4/\text{H}_2\text{O}_2$ proved that the polymers did indeed possess a triblock structure and indirectly provided additional proof for the difunctionality ($F_n = 2.0$) of the telechelic polymers. Notably, the tandem ROMP-ATRP approach first reported successful synthesis of polymethylmethacrylate-polybutadiene-polymethylmethacrylate triblock polymers with a 100% 1,4-polybutadiene microstructure. The methacrylate and epoxide end-functionalized telechelic polybutadienes were thermally or photochemically cross-linked to form polymeric network materials with enhanced thermal stabilities. The incorporation of methacrylate and epoxy end groups using a metathesis approach is a remarkable testament to the synthetic utility of the Ru metathesis catalysts.

Tamura and coworkers reported a Ru-catalyzed ADMET polymerization of 1,9-decadiene in the presence of various ester-containing terminal olefins to afford telechelic polymers [57]. The number of methylene spacers between the olefin and the ester varied; however, no major influence (i.e., no negative neighboring group effects) was observed, which was attributed to the high functional group tolerance

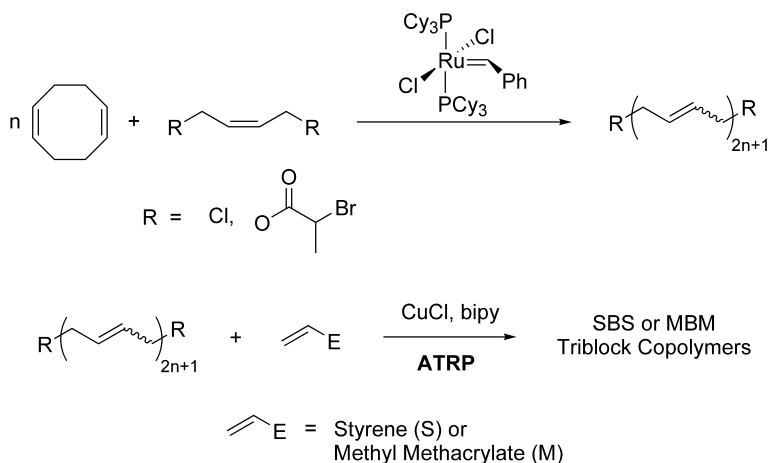


Fig. 3.8-11. Synthesis of ABA triblock copolymers employing a combined metathesis/ATRP approach. Bielawski, C. W.; Morita, T.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 678.

of the Ru catalyst. Optimal conditions for the reaction were 90 °C, a monomer-to-catalyst ratio of 400:1, and a monomer-to-chain-transfer agent ratio of 5:1. Interestingly, the polydispersities of the resultant polymers (M_n values were 4–8 kg mol⁻¹) were quite low (PDI = 1.1 to 1.4). Furthermore, even though terminal olefins (both CTA and monomer) were employed, the isolated polymer contained little to no terminal ethylene units, which further demonstrated the high fidelity of the catalyst in these types of reactions. Tamura later extended this approach to the synthesis of epoxide end-functionalized telechelic polymers [58]. Upon addition of toluene diisocyanate, these pre-polymers were chain extended to rapidly form materials of high molecular weight.

Building from their previous synthetic routes to telechelic oligomers, Wagener and coworkers reported the synthesis of methoxydimethylsilane and chlorodimethylsilane end-functionalized telechelic polyoctenamers using Ru catalysts [59]. For comparison, the polymerizations were performed using a Mo metathesis catalyst as well. 5-Hexenyl-methoxydimethylsilane or 5-hexenyl-chlorodimethylsilane were employed as chain-transfer agents during the ADMET of 1,9-decadiene and were found to not adversely affect the (Ru or Mo) catalyst's stability or activity. Furthermore, no major difference in molecular weight or polydispersity of the telechelic polymers was observed with either catalyst. As with other systems, the molecular weight of the telechelic polymers was easily tuned by adjusting the initial monomer-to-chain-transfer agent ratio. Either of the chain-transfer agents listed above afforded similar results, and, importantly, the chlorine-silicon bond remained intact during the polymerization. However, measured molecular weights were slightly higher than their theoretical values, which may be related to the low reactivity of the olefinic dimer. The functionality of the polymers was judged to be at least 98% difunctional ($F_n \approx 2.0$) by NMR spectroscopy. Polydimethylsiloxane-

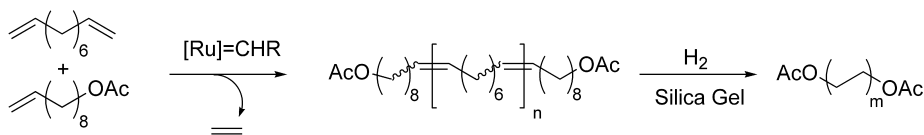


Fig. 3.8-12. Preparation of telechelic polyethylene using a one-pot procedure and a ruthenium metathesis catalyst. Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, 33, 3196.

containing ABA triblock copolymers were subsequently prepared by reacting a PDMS oligomer, which contained a hydroxy end group, with the silyl chloride telechelic polyoctenamer. A unimodal distribution in the resultant SEC chromatograph suggested efficient triblock formation. Furthermore, the final molecular weight of the polymer was found by vapor phase osmometry to be 8.6 kg mol^{-1} , which was the exact value expected based on the molecular weights of the individual homopolymers. Such polymers may find use as thermoplastic elastomers with enhanced adhesive properties.

Watson and Wagener reported a tandem homogeneous metathesis/heterogeneous hydrogenation approach to acetoxy end-functionalized telechelic polyethylenes [60]. In this approach, a Ru alkylidene was converted *in situ* to a Ru hydride. In other words, one catalyst was used for both olefin metathesis and hydrogenation. ADMET of bulk 1,9-decadiene in the presence of 9-decenyl acetate as the chain-transfer agent was used to form the corresponding telechelic polymer. Upon completion of the metathesis reaction, excess silica gel was added and the entire reaction vessel was placed under H_2 pressure (120 psig), which resulted in complete backbone saturation (Figure 3.8-12). The silica gel was necessary to prevent the catalyst dimerization under H_2 that ultimately leads to premature decomposition. Interesting model ethylene/CO copolymers were also produced by using this methodology.

Deming and Brzezinska reported a novel approach to triblock copolymers composed of synthetic and peptidic polymeric segments using telechelic polymers prepared via metathesis [61]. Bis-phthalimide end-functionalized telechelic polyoctenamers were prepared by ADMET of 1,9-decadiene in the presence of 11-phthalimido-1-undecene and a Ru catalyst (Figure 3.8-13). The phthalimide groups were removed with excess hydrazine, liberating the respective amino end-functionalized telechelic polymers. After installing amido-amidate nickelacycles (the active intermediates in *N*-carboxyanhydride polymerizations) onto ends of the polymer chains, the telechelic polymers were used as macroinitiators for the living polymerization of benzyl-L-glutamic acid-*N*-carboxyanhydride (Glu-NCA) to form the respective ABA triblock copolymers. Excellent molecular weight control over both A and B segments of the copolymer was achievable. The polyoctenamer segment was controlled by varying the monomer-to-chain-transfer agent ratio, whereas the peptide segment was controlled by varying the monomer-to-macroinitiator ratio. Polymers with molecular weights up to 12.6 kg mol^{-1} and PDIs = 1.7 were prepared. These copolymers are expected to find use as protein

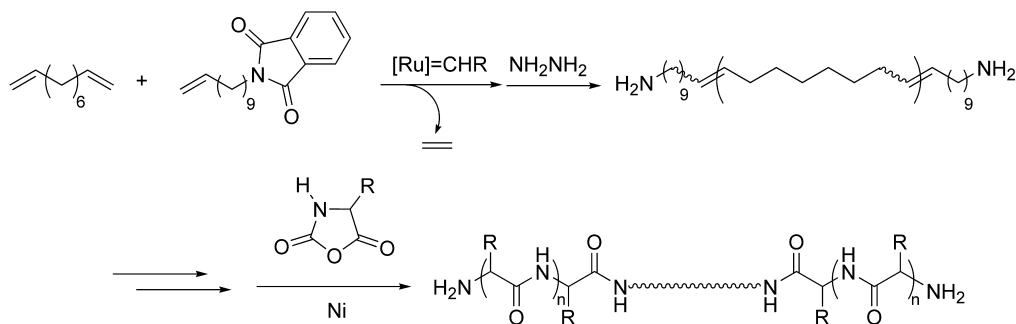


Fig. 3.8-13. Synthesis of ABA triblock copolymers containing polypeptide segments using amino end-functionalized telechelic polymers produced by ADMET polymerization. Brzezinska, K. R.; Deming, T. *Macromolecules* **2001**, 34, 4348.

membrane mimics that may aid in understanding protein-lipid bilayer interactions.

Recently, several new, highly active ruthenium catalysts that utilize *N*-heterocyclic carbene ligands have been reported [62–64]. In particular, they display an unsurpassed level of activity and functional group tolerance in ring-closing metathesis (RCM), cross-metathesis (CM), and ring-opening metathesis polymerization (ROMP) when compared to other Ru catalysts. The high activity and increased functional group tolerance of these catalysts are expected to widen the array of telechelic polymers prepared using olefin metathesis. Lower catalyst loadings, the use of more hindered monomers, and the use of highly functionalized CTAs are just some of the advantages these catalysts are expected to provide.

For example, one drawback of the previously discussed route to hydroxy end-functionalized telechelic polybutadiene using the bis-phosphine ligated Ru catalyst and protected chain-transfer agents is the necessity of a post-polymerization deprotection step [53]. Chain-transfer agents that contained free alcohols lead to unwanted side reactions. However, using the latest generation of highly active Ru catalysts, hydroxy end-functionalized telechelic polybutadienes were prepared in one step using 2-butene-1,4-diol as the chain-transfer agent in conjunction with cyclooctadiene (Figure 3.8-14) [65]. Furthermore, the high activity of the catalyst permitted acetoxy end-functionalized telechelic polybutadienes (using 1,4-diacetoxy-2-butene as the chain-transfer agent and cyclooctadiene as the monomer) with molecular weights controllable up to 30 kg mol⁻¹ to be prepared using monomer-to-catalyst ratios as high as 98,000. Extensive chain transfer is believed to occur with these catalysts, as the telechelic polybutadienes were found to contain a predominately *trans* geometry (up to 90%).

The high activity of the catalyst also permitted the synthesis of telechelic polynorbornenes bearing acetoxy and hydroxy end groups [66]. As noted above, telechelic polynorbornenes were first prepared by Fontanille using olefin metathesis [28]. However, in their report, the molecular weight of the polymers did not

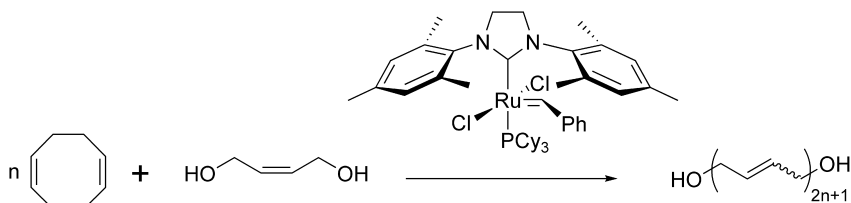


Fig. 3.8-14. Direct synthesis of hydroxy end-functionalized telechelic polybutadienes by a metathesis/chain-transfer process using an unprotected hydroxyl-containing chain-transfer agent. Bielawski, C. W.; Scherman, O. A.; Grubbs, R. H. *Polymer* **2001**, 42, 4939.

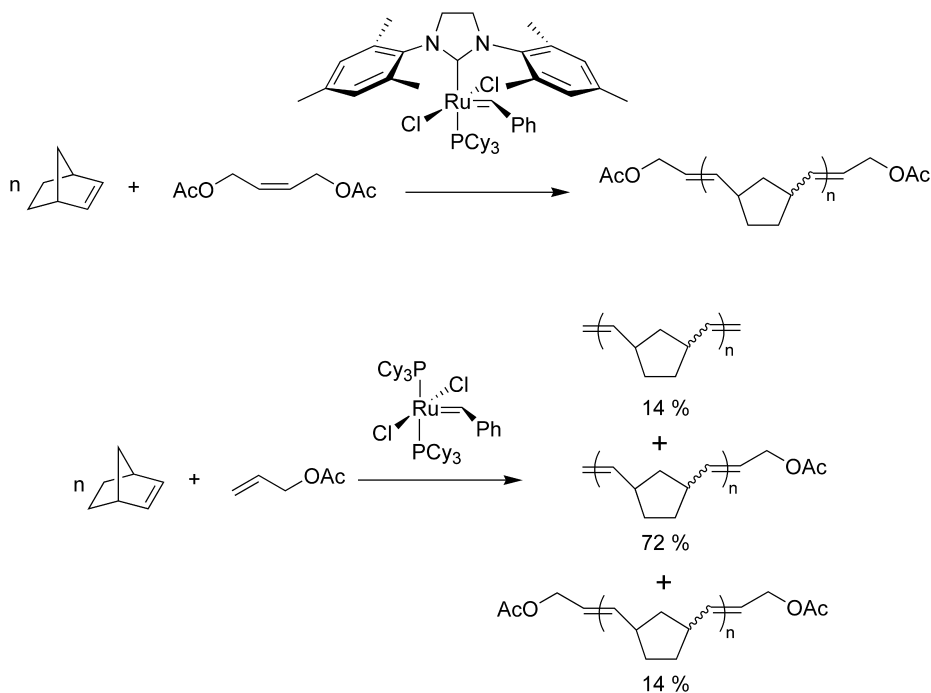


Fig. 3.8-15. Synthesis of telechelic and semi-telechelic polynorbornenes via a ROMP/chain-transfer mechanism using various Ru-containing catalysts and chain-transfer agents. Bielawski, C. W.; Benitez, D.; Morita, T.; Grubbs, R. H. *Macromolecules* **2001**, 34, 8610.

agree with their theoretical values, and large excesses of chain-transfer agent were required to achieve satisfactory control. In contrast, molecular weights were in excellent agreement with their theoretical values (based on the initial monomer-to-chain-transfer agent ratio) when highly active Ru catalysts coordinated with N-heterocyclic carbenes were used (Figure 3.8-15). Acetoxy end-functionalized

polynorbornenes were also obtained by degradation of (commercially available) high-molecular-weight polynorbornene. Removal of the acetoxy groups afforded the corresponding hydroxy end-functionalized polymers with F_n values near 2.0 (as determined by titrimetric methods). For comparison, semi-telechelic polynorbornenes with an acetoxy group at one terminus and a vinyl group at the other were prepared using norbornene, the less active Ru-based olefin metathesis catalyst $(PCy_3)_2Cl_2Ru=CHPh$, and allyl acetate as a chain-transfer agent. In this case, the reaction appears to be governed by relative rates of reaction between the catalyst and the monomer or chain-transfer agent.

3.8.3.3

Synthesis of End-Functionalized Polymers Using Functionalized Initiators

Nearly all of the metathetical approaches to telechelic polymers described above rely on the ability of the catalyst to efficiently facilitate chain transfer. However, in many cases, the catalyst does not possess enough activity to do so, and the preparation of telechelic polymers becomes a kinetically controlled process governed by the relative rates of polymerization and chain transfer. Ozawa capitalized on this phenomenon for the preparation of semi-telechelic polymers, where only one end of the polymer chains is functionalized, using asymmetrical chain-transfer agents and Ru vinylidene complexes [67, 68]. Functionalized olefins such as vinyl ethers and vinyl sulfides are known to react regioselectively with Ru alkylidenes (i.e., $[Ru]=CHR$, $R = Ph$, alkyl) and Ru vinylidenes (i.e., $[Ru]=C=CHR$) to afford the corresponding Fischer carbene complexes $[Ru]=CHE$, $E = SR$, OR [69]. Although less active than their alkylidene counterparts, such Fischer carbene complexes are capable of initiating the ROMP of strained cyclic olefins such as norbornene. Thus, the Ru vinylidene initially reacts with the terminal olefin to form the Fischer carbene complex, which subsequently initiates the ROMP of norbornene. After a certain amount of monomer has been polymerized, chain transfer to the CTA regenerates the Fischer carbene complex and yields the end-functionalized polymer (Figure 3.8-16). Extensive NMR spectroscopic analysis verified that the polymers did indeed contain only one functional group per polymer chain (i.e., $F_n = 1$). However, the polydispersity index values of the resultant polymers were rather broad, and, although tunable, the molecular weights did not correlate with the initial monomer-to-chain-transfer agent ratios. These two observations suggested that the reaction might be under kinetic control. Regardless of the mechanism, ethyl vinyl ether, phenyl vinyl sulfide, and *N*-pyrrolidinone were used to prepare the corresponding end-functionalized polynorbornenes with M_n values up to 15 kg mol^{-1} . The vinyl ethoxy end-functionalized polynorbornenes were later hydrogenated to form the corresponding polynorboranes or hydrolyzed under acidic conditions to install aldehyde end groups. The authors later used the same approach to prepare polynorbornenes with an atom transfer radical polymerization (ATRP) initiator end group. These polymers were subsequently employed as macroinitiators for polymerization of styrene or methyl methacrylate to form the respective diblock copolymers [70].

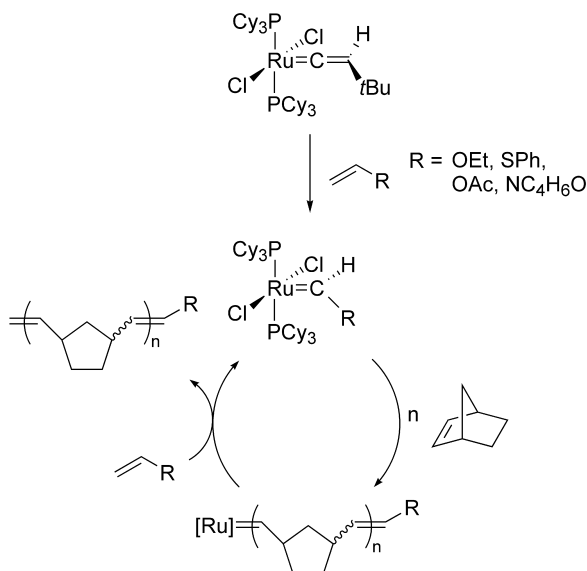


Fig. 3.8-16. Synthesis of semi-telechelic polynorbornenes.
Katayama, H.; Urushima, H.; Ozawa, F. J. *Organometallic Chem.*
2000, 606, 16.

Likewise, living polymerizations have also been used to prepare semi-telechelic polymers. Titanacyclobutanes were the first reported catalysts that could be used for living ROMP [71]. It was known at that Ti carbenes reacted with aldehydes, ketones, and esters to give Wittig-type products in high yield [72, 73]. This feature was exploited to prepare end-functionalized polynorbornenes. At the conclusion of a Ti-mediated ROMP of norbornene, excess benzophenone was added to afford a diphenylethylene end-capped polymer. A similar approach was employed by Schrock and coworkers using Mo catalysts and appropriately functionalized aldehydes. They prepared a series of end-functionalized redox-active polynorbornenes that were later covalently attached to surfaces [74, 75].

Gibson and coworkers demonstrated that treatment of a Ru-mediated living ROMP of amide- and ester-functionalized norbornenes with molecular oxygen afforded polymers possessing a single aldehyde group positioned at only one end of the polymer chain [76]. Kiessling and coworkers used living ROMP to prepare polynorbornenes with a single fluorescent group at only one end of the polymer chain by adding a bifunctional capping reagent, which essentially was a derivatized vinyl ether, at the end of a Ru-mediated ROMP. Such polymers were found to be useful in cellular binding assays for L-selectin, a cell surface protein [77, 78].

Living polymerizations can also be used to prepare telechelic polymers. Matching the functional group delivered by the initiator with that of a terminating or chain-transfer reagent permits the synthesis of a symmetrically end-functionalized polymer. Gibson and Okada used this approach for the synthesis of acetoxy and hydroxy end-functionalized telechelic polybornene derivatives (Figure 3.8-17) [79].

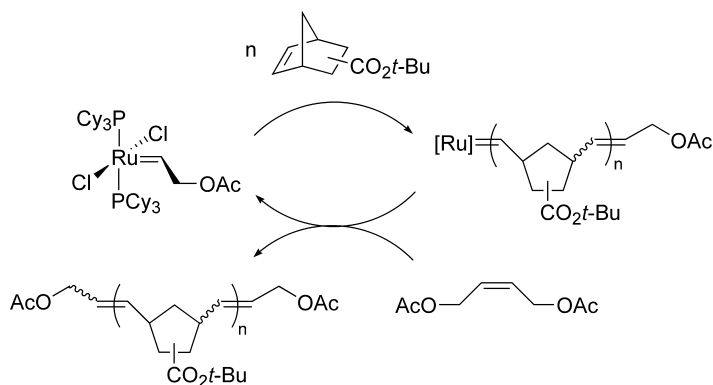


Fig. 3.8-17. Synthesis of telechelic polynorbornenes using a functionalized Ru initiator. Gibson, V. C.; Okada, T. *Macromolecules* **2000**, 33, 655.

The functionalized Ru catalyst, $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHCH}_2\text{OAc}$, was independently synthesized and employed as the initiator for the living ROMP of a *tert*-butylester-functionalized norbornene. This initiator placed an acetoxy group at one end of the polymer chain and an active (i.e., propagating) Ru species on the other end. After all the monomer was polymerized, 1,4-diacetoxy-2-butene was added, which effectively transferred an acetoxy group from the chain-transfer agent to the end of the growing polymer chain, thereby forming a telechelic polymer (as well as regenerating the Ru initiator).

By using a “pulsed addition” variation of this approach, multiple batches of telechelic polymer could be prepared in a single reaction vessel by successively adding batches of monomer [80, 81]. For example, after polymerizing 100 equivalents of the norbornene derivative and adding the chain-transfer agent, another 400 equivalents of monomer (followed by chain-transfer agent) were added to form a second polymer within the same reaction vessel. Two polymers with distinct molecular weights were observed in the size-exclusion chromatogram, each with narrow polydispersities and molecular weights corresponding to polymers with 100 and 400 monomer units, respectively. This process was shown to be repeatable, demonstrating the high fidelity of the Ru catalysts and providing an efficient means to tailor polymeric blends. A basic workup of the telechelic polymer reduced the acetoxy groups and formed the hydroxy end-functionalized derivative. Furthermore, the polymers were hydrogenated to afford end-functionalized telechelic polyolefin-like materials.

3.8.4

Conclusions and Outlook

More than two decades have passed since the initial reports that described the preparation of end-functionalized telechelic polymers using olefin metathesis

[20, 24]. ROMP, ADMET, and metathesis degradation have all played key roles in their preparation. While their mechanistic steps differ, the incorporation of a chain-transfer agent into a polymer chain is a key requirement. This process generally occurs through transfer of a reactive polymeric species to a suitable chain-transfer agent followed by subsequent incorporation into a polymer chain either by additional polymerization or through intermolecular reaction. In that respect, the nature of the metathesis catalyst is of central importance, and this chapter was divided along the lines of “classical” and “well-defined” systems. From an economic standpoint, one may argue that simple metathesis catalysts such as $\text{WCl}_6/\text{SnMe}_4$ are more attractive for the synthesis of telechelic polymers. However, their low functional group tolerance and the need to employ relatively high catalyst loadings drastically limit their practical application. While advances in well-defined W and Mo systems have certainly overcome several of these limitations, Ru-based systems appear to have the most advantages. They possess extraordinary functional group tolerance, display an unprecedented level of activity, and are now commercially available. Collectively, these features make the Ru systems competitive in all aspects [64]. Furthermore, the use of Ru-based catalysts provides several options for curtailing many of the shortcomings associated with catalysts based on other transition metals. For example, non-functional end groups from the catalyst initiating/terminating processes may now be minimized by using minute amounts of catalyst [65], functionalized initiators [79], or specially functionalized end-capping reagents [77]. These features in combination with a remarkable functional group tolerance [65] have ultimately made Ru-based catalysts a highly desirable choice for preparing telechelic polymers.

References

- 1 GOETHALS, E. J. *Telechelic Polymers: Synthesis and Applications*; CRC Press: Boca Raton, FL, 1989.
- 2 HEPBURN, C. *Polyurethane Elastomers*; Elsevier Applied Science: New York, 1992.
- 3 KRESTA, J. E.; ELDERED, E. W. *60 Years of Polyurethanes*; CRC Press: New York, 1998.
- 4 MACOSKO, C. W. *RIM, Fundamentals of Reaction Injection Molding*; Hanser Publishers: New York, 1989.
- 5 HOLDEN, G.; LEGGE, N. R.; QUIRK, R. P.; SCHROEDER, H. E. *Thermoplastic Elastomers*; 2nd ed.; Hanser/Gardner, 1993.
- 6 YAMAUCHI, K.; LIZOTTE, J. R.; HERCULES, D. M.; VERGNE, M. J.; LONG, T. E. J. *Am. Chem. Soc.* **2002**, 124, 8599.
- 7 KILBINGER, A. F. M.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2002**, 41, 1563.
- 8 MATYJASZEWSKI, K.; XIA, J. H. *Chem. Rev.* **2001**, 101, 2921.
- 9 HSIEH, H. L.; QUIRK, R. P. *Anionic Polymerization: Principles and Practical Applications*; Marcel Dekker: New York, 1996.
- 10 MATYJASZEWSKI, K. *Cationic Polymerizations: Mechanisms, Synthesis, and Applications*; Marcel Dekker: New York, 1996.
- 11 For example see: FRICK, E. M.; HILLMYER, M. A. *Macromol. Rapid Commun.* **2000**, 21, 1317.
- 12 IVIN, K. J. *Olefin Metathesis*; Academic Press: London, 1983.
- 13 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, 1991.
- 14 The presence of cyclics lower the F_n for a given telechelic polymer because while they contribute to the total number of chains, they are non-functional. However, they are not

- as detrimental in a subsequent condensation polymerization (for example, polyurethane synthesis) as a monofunctional telechelic polymer since cyclic oligomers are effectively unreactive. Therefore, if the F_n is low because of the presence of macrocycles, higher concentrations can be used to account for the difference.
- 15 We acknowledge that in ADMET polymerizations, vinyl end groups are produced "by default". By definition these are telechelic polymers, but do not fall under the types of macromolecules emphasized in this chapter.
 - 16 PAMPUS, G.; WITTE, J.; HOFFMAN, M. *Rev. Gen. Caoutch. Plast.*, **1970**, *47*, 1344.
 - 17 PINAZZI, C.; REYX, C. R. *Acad. Sci., Ser. C*. **1973**, 272, 1077.
 - 18 PINAZZI, C.; GUILMET, I.; REYX, D. *Tetrahedron Lett.* **1976**, *13*, 989.
 - 19 PINAZZI, C.; CAMPISTRON, I.; REYX, D. *Bull. Soc. Chim. Fr.* **1977**, *9*, 896.
 - 20 REYX, D.; HAMZA, M.; CAMPISTRON, I. *J. Mol. Cat.* **1980**, *42*, 289.
 - 21 MASS, A. J., DALE, A. I.; TIGHE, B. J. *Makromol. Chem.* **1982**, *183*, 1731.
 - 22 PINAZZI, C. P.; CAMPISTRON, I.; CROISSANDEAU, M. C.; REYX, D. *J. Mol. Cat.* **1980**, *8*, 325.
 - 23 REYX, D.; CAMPISTRON, I.; HEILING, P. *Makromol. Chem.* **1982**, *183*, 173.
 - 24 OTTON, J.; COLLEUILLE, Y.; VARAGNAT, J. *J. Mol. Cat.* **1980**, *8*, 313.
 - 25 REYX, D.; CAMPISTRON, I.; HAMZA, M. *J. Mol. Cat.* **1986**, *36*, 101.
 - 26 REYX, D.; CROISSANDEAU, M. C. *Makromol. Chem.* **1982**, *183*, 1371.
 - 27 SEYFORTH, K.; TAUBE, R.; DAHLKE, M. East. Ger. Pat. 146,053 (1981); *Chem. Abstr.* **1981**, *95*, 43978.
 - 28 CRAMAIL, H.; FONTANILLE, M.; SOUM, A. *J. Mol. Cat.* **1991**, *65*, 193.
 - 29 CRAMAIL, H.; FONTANILLE, M.; SOUM, A. *Makromol. Chem. Macromol. Symp.* **1991**, *42/43*, 281.
 - 30 HEROGUEZ, V.; SOUM, A.; FONTANILLE, M. *Polymer* **1992**, *33*, 3302.
 - 31 CHUNG, T. C.; CHASMAWALA, M. *Macromolecules* **1991**, *24*, 3718.
 - 32 CHUNG, T. C. *J. Mol. Cat.* **1992**, *76*, 15.
 - 33 CHUNG, T. C.; RAMAKRISHNAN, S.; KIM, M. W. *Macromolecules* **1991**, *24*, 2675.
 - 34 RAMAKRISHNAN, S.; CHUNG, T. C. *Macromolecules* **1990**, *23*, 4519.
 - 35 CHUNG, T. C.; CHASMAWALA, M. *Macromolecules* **1992**, *25*, 5137.
 - 36 CHASMAWALA, M.; CHUNG, T. C. *Macromolecules* **1995**, *28*, 1333.
 - 37 NUBEL, P. O.; YOKELSON, H. B., LUTMAN, C. A., BOUSLOG, W. G., BEHREND, R. T., RUNGE, K. D. *J. Mol. Cat. A: Chem.* **1997**, *115*, 43.
 - 38 ICHIKAWA, K.; FUKUZUMI, K. *J. Org. Chem.* **1976**, *41*, 2633.
 - 39 NUBEL, P. O.; LUTMAN, A.; YOKELSON, H. B. *Macromolecules* **1994**, *27*, 7000.
 - 40 HILLMYER, M. A.; GRUBBS, R. H. *Macromolecules* **1993**, *26*, 872.
 - 41 For a relevant example see: FU, G. C.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.
 - 42 WAGENER, K. B.; BRZEZINSKA, K. *Macromolecules* **1991**, *24*, 5273.
 - 43 HILLMYER, M. A.; GRUBBS, R. H. *Macromolecules* **1995**, *28*, 8662.
 - 44 MARMO, J. C.; WAGENER, K. B. *Macromolecules* **1993**, *26*, 2137.
 - 45 MARMO, J. C.; WAGENER, K. B. *Macromolecules* **1995**, *28*, 2602.
 - 46 SUTER, U. W.; HÖCKER, H. *Makromol. Chem.* **1988**, *189*, 1603.
 - 47 MARMO, J. C.; WAGENER, K. B. *Macromol. Rapid. Commun.* **1995**, *15*, 557.
 - 48 VISWANATHAN, T.; GOMEZ, F.; WAGENER, K. B. *J. Polym. Sci., Polym. Chem.* **1994**, *32*, 2469.
 - 49 FRASER, C.; HILLMYER, M. A.; GUTIERREZ, E.; GRUBBS, R. H. *Macromolecules* **1995**, *28*, 7256.
 - 50 HILLMYER, M. A. The Preparation of Functionalized Polymers by Ring-Opening Metathesis Polymerization. Ph.D. Dissertation, California Institute of Technology, Pasadena, CA, 1995.
 - 51 NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.
 - 52 NGUYEN, S. B. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858.
 - 53 HILLMYER, M. A.; NGUYEN, S. T.; GRUBBS, R. H. *Macromolecules* **1997**, *30*, 718.

- 54 BIELAWSKI, C. W.; MORITA, T.; GRUBBS, R. H. *Macromolecules* **2000**, *33*, 678.
- 55 MORITA, T.; MAUGHON, B. R.; BIELAWSKI, C. W.; GRUBBS, R. H. *Macromolecules* **2000**, *33*, 6621.
- 56 MAUGHON, B. R.; MORITA, T.; BIELAWSKI, C. W.; GRUBBS, R. H. *Macromolecules* **2000**, *33*, 1929.
- 57 TAMURA, H.; MAEDA, N.; MATSUMOTO, R.; NAKAYAMA, A.; HAYASHI, H.; IKUSHIMA, K.; KURAYA, M. J. *Macromol. Sci. Pure Appl. Chem.* **1999**, *36*, 1153.
- 58 TAMURA, H.; NAKAYAMA, A. J. *Macromol. Sci. Pure Appl. Chem.* **2002**, *A39*(7), 745.
- 59 BRZEZINSKA, K. R.; WAGENER, K. B.; BURNS, G. T. J. *Polym. Sci., Polym. Chem.* **1999**, *37*, 849.
- 60 WATSON, M. D.; WAGENER, K. B. *Macromolecules* **2000**, *33*, 3196.
- 61 BRZEZINSKA, K. R.; DEMING, T. *Macromolecules* **2001**, *34*, 4348.
- 62 HUANG, J.; SCHANZ, H.-J.; STEVENS, E. D.; NOLAN, S. P. *Organometallics* **1999**, *18*, 5375.
- 63 SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953.
- 64 BIELAWSKI, C. W.; GRUBBS, R. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 2903.
- 65 BIELAWSKI, C. W.; SCHERMAN, O. A.; GRUBBS, R. H. *Polymer* **2001**, *42*, 4939.
- 66 BIELAWSKI, C. W.; BENITEZ, D.; MORITA, T.; GRUBBS, R. H. *Macromolecules* **2001**, *34*, 8610.
- 67 KATAYAMA, H.; URUSHIMA, H.; OZAWA, F. *Chem. Lett.* **1999**, 369.
- 68 KATAYAMA, H.; URUSHIMA, H.; OZAWA, F. J. *Organomet. Chem.* **2000**, *606*, 16.
- 69 LOUIE, J.; GRUBBS, R. H. *Organometallics* **2002**, *21*, 2153.
- 70 KATAYAMA, H.; YONEZAWA, F.; NAGAO, M.; OZAWA, F. *Macromolecules* **2002**, *35*, 1133.
- 71 CANNIZZO, L. F.; GRUBBS, R. H. *Macromolecules* **1987**, *20*, 1488.
- 72 CANNIZZO, L. F.; GRUBBS, R. H. J. *Org. Chem.* **1985**, *50*, 2316.
- 73 PINE, S. H.; ZAHLER, R.; EVANS, D. A.; GRUBBS, R. H. J. *Am. Chem. Soc.* **1980**, *102*, 3270.
- 74 ALBAGLI, D.; BAZAN, G. C.; SCHROCK, R. R.; WRIGHTON, M. S. J. *Am. Chem. Soc.* **1993**, *115*, 7328.
- 75 ALBAGLI, D.; BAZAN, G. C.; SCHROCK, R. R.; WRIGHTON, M. S. J. *Phys. Chem.* **1993**, *97*, 10211.
- 76 BIAGINI, S. C. G.; DAVIES, R. G.; GIBSON, V. C.; GILES, M. R.; MARSHALL, E. L.; NORTH, M. *Polymer* **2001**, *42*, 6669.
- 77 GORDON, E. J.; GESTWICKI, J. E.; STRONG, L. E.; KIESSLING, L. L. *Chem. Biol.* **2000**, *7*, 9.
- 78 OWEN, R. M.; GESTWICKI, J. E.; YOUNG, T.; KIESSLING, L. L. *Org. Lett.* **2002**, *14*, 2293.
- 79 GIBSON, V. C.; OKADA, T. *Macromolecules* **2000**, *33*, 655.
- 80 CROWE, W. E.; MITCHELL, J. P.; GIBSON, V. C.; SCHROCK, R. R. *Macromolecules* **1990**, *23*, 3534.
- 81 SCHROCK, R. R.; YAP, K. B.; YANG, D. C.; SITZMANN, H.; SITA, L. R.; BAZAN, G. C. *Macromolecules* **1989**, *22*, 3191.

3.9

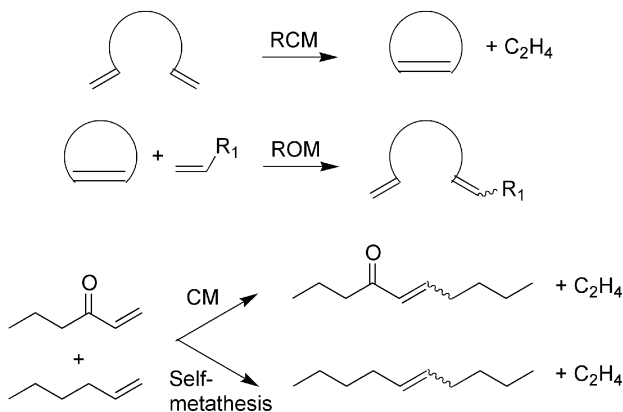
ADMET Polymerization

Stephen E. Lehman, Jr. and Kenneth B. Wagener

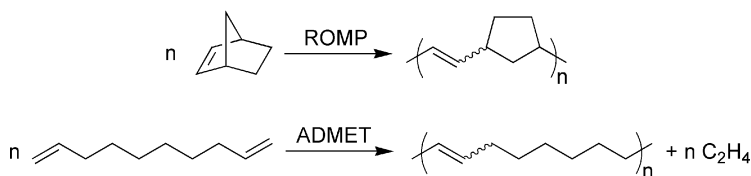
3.9.1

Introduction

Olefin metathesis is a stunning example of the successful application of organo-metallic chemistry in both academic and industrial settings. Metathesis refers to exchange of atoms of different molecules, and thus olefin metathesis is a chemical transformation causing the apparent exchange of the substituents of olefins to form new olefins [1]. Modern olefin metathesis is a mild method of forming carbon-carbon double bonds and can be conducted in several distinct reaction modes (Scheme 3.9-1). Ring-closing metathesis (RCM) is the unimolecular condensation reaction of a diene to form a cyclic olefin and a small condensate olefin as a byproduct, and it has been used extensively in critical ring-closure steps in the synthesis of sophisticated organic molecules [2–8]. Chiral catalysts recently have been developed that perform asymmetric RCM (ARCM), in which only one enantiomer of a racemic substrate is ring closed or an achiral substrate is ring closed chiroselectively to give a product with high enantiopurity [9, 10]. Cross-metathesis (CM) is the reaction of two acyclic olefins to form two new olefins [11–14]. Of



Scheme 3.9-1. Olefin metathesis reactions for synthetic organic chemistry.



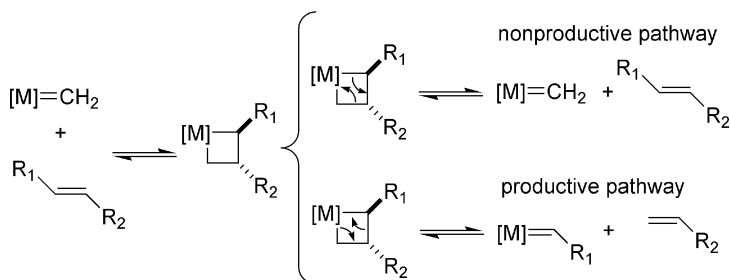
Scheme 3.9-2. Olefin metathesis polymerization modes.

critical importance to CM is the selectivity of the reaction, specifically the preference of forming the so-called cross-product over the products of self-metathesis, which is the metathesis of two identical molecules to form a metathesis “dimer” (note that the term “dimer” in the context of metathesis is misleading in that not all atoms of the starting material are present in the dimer). Ring-opening metathesis (ROM) is the reverse reaction of RCM, in which a cyclic olefin is reacted with an acyclic olefin to produce a new acyclic diene [15–17]. Indeed, olefin metathesis is now considered a reliable tool for the organic chemist.

Olefin metathesis has been equally successful in polymer synthesis. There are two modes of olefin metathesis polymerization: ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis polymerization (ADMET) (Scheme 3.9-2). ROMP is a popular chain polymerization that is thermodynamically driven by the release of ring strain in a cyclic olefin monomer [18]. Under appropriate conditions with certain catalysts, ROMP can be controlled to such an extent that it satisfies the criteria of living polymerization [19, 20]. ADMET is a condensation polymerization and is essentially the self-metathesis of a diene, usually a terminal diene, to form high polymer [21]. This chapter will focus on ADMET polymerization with emphasis on the scope and limitations of the polymerization, details of the catalysis, and application of this reaction.

Olefin metathesis is always a metal-catalyzed transformation, and the history of olefin metathesis is fascinating [22]. Unlike many chemical reactions, olefin metathesis had its start in an industrial setting, and the early catalyst mixtures were based on high oxidation state metal salts or complexes and an appropriate activating agent, such as an alkyl aluminum or tin compound or a main-block oxide. Supported oxide catalysts (i.e., $\text{MoO}_3/\text{Al}_2\text{O}_3$) were commonly employed for cross-metathesis and related reactions, and Ziegler-Natta-type mixtures (i.e., $\text{MoCl}_5/\text{Et}_3\text{Al}$) were used for ROMP. Some salts or complexes of late-transition metals were also found to promote olefin metathesis with or without an activating agent, particularly those of rhenium [23] and ruthenium [24]. These “classical” catalysts were employed industrially for several processes and polymerizations [25]. The observation by Calderon that the $\text{WCl}_6/\text{EtAlCl}_2/\text{EtOH}$ catalyst system would promote both ROMP [26] and olefin disproportionation [27–29] led to the recognition that the same reaction was responsible for both chemical transformations. The catalytic species responsible for metathesis with these classical catalyst mixtures were not spectroscopically identifiable due in part to low solution concentrations of active species. Therefore, these mixtures are referred to as “ill-defined” catalysts.

Several mechanisms were actively debated in the literature during the 1970s, but

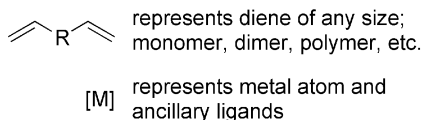


Scheme 3.9-3. The metal-carbene mechanism of metathesis, productive and non-productive pathways shown; $[M]$ refers to the metal atom and associated ligands.

the proposition known as the Chauvin mechanism [30] was the most consistent with observation [31]. Isotopic labeling, kinetics, and product distribution studies for the metathesis of acyclic olefins [32–39] were particularly useful in establishing the validity of this mechanism. All of the characteristics of ROMP are also consistent with the Chauvin mechanism [40]. This mechanism involves the intermediacy of metallacyclobutanes and metal carbenes, which are metal complexes containing a metal-carbon double bond.

The catalytic cycle for the Chauvin mechanism of olefin metathesis (Scheme 3.9-3) begins with a metal-carbene complex undergoing a 2+2 cycloaddition with an olefin to form a metallacyclobutane, which then decomposes by 2+2 retrocycloaddition. If the metallacyclobutane decomposes in exactly the reverse manner as the formation of the metallacyclobutane, then the reaction sequence is degenerate and the starting materials are simply regenerated. However, if the decomposition proceeds in the other possible regiochemical course, then a new olefin and a new metal-carbene complex result, and the reaction is termed “productive” (Scheme 3.9-3).

The mechanism of productive ADMET polymerization of an α,ω -diene, that is, the sequence of reactions that lead to polymer, involves two distinct types of metal-carbene species: the metal methylidene and various metal alkylidenes (Scheme 3.9-4). Metathesis of a terminal olefin with a metal methylidene complex produces a molecule of ethylene and a metal alkylidene via the α -substituted metallacyclobutane, where the terminal olefin can be monomer, dimer, polymer, etc. The metal alkylidene thus generated then undergoes metathesis with another terminal olefin to produce the “coupled” internal olefin and the metal methylidene, via the α,β -disubstituted metallacyclobutane. This new metal methylidene then begins another productive metathesis cycle. Obviously there are many other metathesis pathways that do not lead to polymer, including degenerate metathesis reactions and depolymerization by reaction with ethylene. All evidence suggests that all of these pathways occur to some degree and that elimination of gaseous ethylene from the polymerization is the driving force for the productive pathway. All experimentation with ADMET has been consistent with the Chauvin mechanism for olefin metathesis.

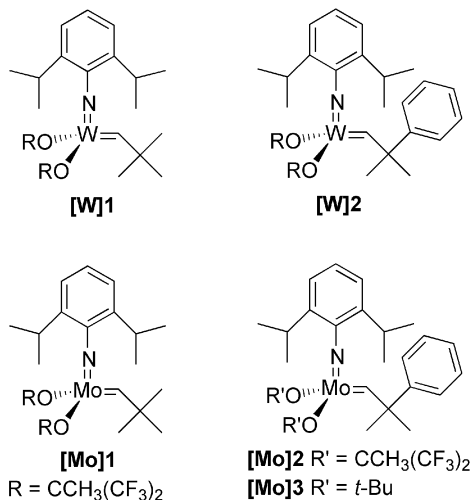


Scheme 3.9-4. Mechanism of productive ADMET.

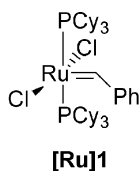
Discoveries were made in the mid- to late 1980s and early 1990s that brought the understanding of olefin metathesis to a much more complete level. Grubbs and coworkers described spectroscopically characterizable titanacyclobutanes that promote living ROMP via high-energy titanium carbenes [41–46]. In pivotal work, Schrock and coworkers, for whom this type of metal carbene is named [47], developed neutral and Lewis-acid-free complexes of tungsten [48–50] and molybdenum [51–53] that contained metal-carbon double bonds and were quite active for olefin metathesis. These carbene complexes are referred to as “well-defined” catalysts in contrast to the “ill-defined” classical catalysts, since the catalytically active species are spectroscopically identifiable. The fact that these complexes were highly active for both olefin metathesis of acyclic olefins and the ROMP of cyclic olefins did much to confirm the intermediacy of metal carbenes in olefin metathesis. In addition, tungstacyclobutanes and molybdacyclobutanes resulting from the reaction of these complexes with certain olefins were isolated and characterized, which validated the involvement of metallacyclobutanes in the mechanism for olefin metathesis. It is noteworthy to mention that although the Schrock well-defined metathesis catalysts are sensitive to air and moisture, these complexes can be prepared in multigram quantities and may be handled using the standard techniques for the manipulation of catalytically air- and moisture-sensitive materials.

A number of achievements in the synthesis of both small molecules and polymers were made possible by the advent of Schrock's catalysts. These catalysts spurred extensive and comprehensive investigations of the utility of RCM in the construction of carbocyclic and heterocyclic compounds [2] and greatly extended

the utility of ROMP and ADMET polymerization, including living ROMP polymerization [19]. The identities of all the ligands are critical to the metathesis activity of these complexes, particularly the electronic properties of the alkoxide ligands. For example, complex **[Mo]2**, with partially fluorinated alkoxide ligands, is highly active for the metathesis of acyclic olefins and uncontrolled ROMP, whereas complex **[Mo]3**, with *t*-butoxy ligands, promotes controlled ROMP and is not highly active for the metathesis of acyclic olefins [19, 52]. Schrock's catalysts **[W]1**, **[W]2**, and **[Mo]2** have been used extensively in ADMET polymerization of hydrocarbon dienes and, to some extent, functionalized dienes.

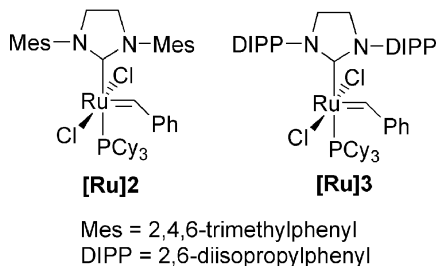


One challenge in the utility of these catalysts is their sensitivity to air and moisture and some protic or polar functional groups. These characteristics are somewhat expected of high oxidation state early-transition metal complexes due to the electrophilicity of the metal atom. Complexes of the late-transition metals are typically less sensitive to air, moisture, and polar or protic functional groups than the early-transition metals because the metal atom is less electrophilic; therefore, there was a general desire to develop olefin metathesis catalysts based on late-transition metals. Schrock and coworkers created well-defined complexes of rhenium that were active for olefin metathesis [54]. Ruthenium, however, has proven to be the most successful late-transition metal for metathesis catalysis [55].



Cy = cyclohexyl

In the early 1990s, Grubbs and coworkers introduced well-defined carbene complexes of ruthenium that were active for olefin metathesis [56–59]. These first-generation ruthenium compounds were considerably less active than the early-transition metal catalysts, but they did not suffer as much as the early-transition metal complexes from exposure to water, oxygen, and coordinating functional groups. Recent developments in the ancillary ligation about the ruthenium have produced complexes with much higher activity than the initially developed ruthenium carbenes. Specifically, substitution of *N*-heterocyclic carbene ligands [60, 61] for one phosphine ligand produces catalysts that are highly active for olefin metathesis reactions and more functional group tolerant than the first-generation ruthenium catalysts [62–65]. In some cases, the activity of these second-generation ruthenium catalysts approaches the activity of Schrock's molybdenum catalyst [66]. In fact, some new ruthenium catalysts can perform high-yielding ring-closing metathesis reactions in undistilled solvents under an atmosphere of air [67]. Developments in this area of metathesis catalyst synthesis are being rapidly disclosed in the literature [68–71].



All of these catalyst developments have made ADMET a useful polymerization reaction. Almost all general aspects of ADMET polymerization can be explained in terms of polycondensation chemistry, and this subject will be discussed in detail. With a firm basis of the fundamental aspects of ADMET polymerization, the details of the catalysis will be discussed in the context first of hydrocarbon dienes and then of functionalized dienes. The kinetics and other mechanistic details of ADMET then will be presented, followed by specific examples of application of ADMET polymerization to the synthesis of useful polymers.

3.9.2

ADMET: The Metathesis Polycondensation Reaction

The fact that acyclic diene metathesis is a condensation polymerization has a number of consequences that differentiate ADMET from the more widely employed chain metathesis polymerization ROMP. It is important to have these aspects of the ADMET reaction in mind before considering the details of the catalysis, as a number of features of the ADMET reaction are illustrated in terms of the condensative nature of this polymerization.

3.9.2.1

Kinetics and Equilibrium Considerations

Condensation polymerizations are usually equilibrium processes in which the functional groups react in a stepwise fashion to form dimer from two monomers, then trimer, tetramer, and so on to high polymer [72]. The result of the stepwise nature of ADMET is that high conversions are necessary to form high-molecular-weight polymer, as expressed by the Carothers equation, in which \bar{X}_n is the number average degree of polymerization (also known as the degree of polymerization, DP) and p is the extent of reaction or conversion of the diene monomer.

$$\bar{X}_n = \frac{1}{1-p} \quad (1)$$

Inspection of the graph of the theoretical \bar{X}_n versus conversion of the monomer shows that conversions in excess of 99% are necessary to form high polymer. Once the polymerization reaches these high conversions, each connection that is made combines two high-molecular-weight polymer chains and thus reduces the number of polymer molecules in the sample by a sizable proportion. This significant reduction in the number of polymer molecules in the sample results in a large increase in the average molecular weight of the polymer chains (Figure 3.9-1,

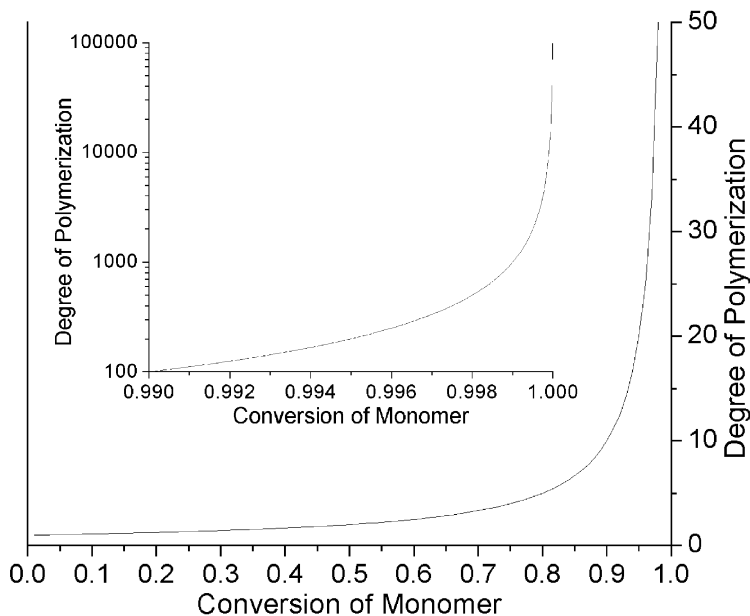
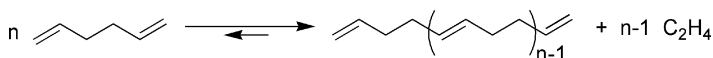


Fig. 3.9-1. Theoretical degree of polymerization vs. conversion of monomer for polycondensation. Inset shows the high conversion region in greater detail (note the logarithmic scale).

inset). This situation is distinctly different from what occurs at lower conversions. More polymer molecules are present in the sample, and each condensation event reduces the number of polymer molecules in the sample by only a small proportion. Thus, the rate of molecular weight growth remains low until high conversions are attained (Figure 3.9-1). In terms of catalysis, this situation requires that the catalyst remain highly active throughout the polymerization cycle.

Many of the modern olefin metathesis catalysts, such as [Mo]2, are more active for terminal olefins than unstrained internal olefins due to the reduced steric hindrance of terminal olefins compared to internal olefins. This trend is reversed for some catalysts, such as [W]1, presumably due to preference of the catalyst for more electron-rich internal olefins. Thus, most monomers for ADMET are terminal dienes, in which the olefins are monosubstituted, in order to ensure that the highest conversion of the terminal olefins is achieved.

Despite the relationship between molecular weight and conversion, many condensation polymerizations are employed successfully on a large scale for commercially important polymers including polyesters, polyamides, and polyimides [73]. The high conversions necessary for high polymer formation are achieved by removal of the condensate molecule from the polymerization. Removal of the condensation product shifts the equilibrium toward high polymer by preventing the reverse reaction to form monomer. (Scheme 3.9-5) Since the condensate molecule for ADMET of α,ω -dienes, ethylene, is a gas that is easily removed from the polymerization at room temperature, ADMET is especially suited for polycondensation in this respect. In contrast, many traditional polycondensations liberate water or alcohols that must be actively removed from the polymerization with heat or vacuum.



Scheme 3.9-5. ADMET equilibrium.

In contrast to the stepwise nature of ADMET, the chain-addition mode of polymerization in ROMP allows for high-molecular-weight polymer chains to be formed at low monomer conversions. This occurs by rapid addition of many cyclic olefin molecules to an active polymer chain before a chain transfer or termination event stops growth of that chain. Thus, for ROMP, high-molecular-weight chains can exist in the presence of a large excess of monomer, a situation that is statistically prohibited by the stepwise condensation mechanism of ADMET. Incidentally, this fact is one of the features of ROMP that supports the Chauvin mechanism for olefin metathesis. Although molecular weights ultimately attainable by ROMP are higher than those by ADMET, molecular weight in excess of 100 kDa often is not a requirement for functionalized polymers. Polar condensation polymers such as polyesters and polyimides become impossible to process into useful structures if the reactions are carried to too high a molecular weight (usually above \bar{M}_n of 30,000 g mol⁻¹). The molecular weights of ADMET polymers, especially function-

alized ADMET polymers, are such that processing the materials is simple and material properties are more than sufficient for application.

3.9.2.2

Molecular Weight Distribution

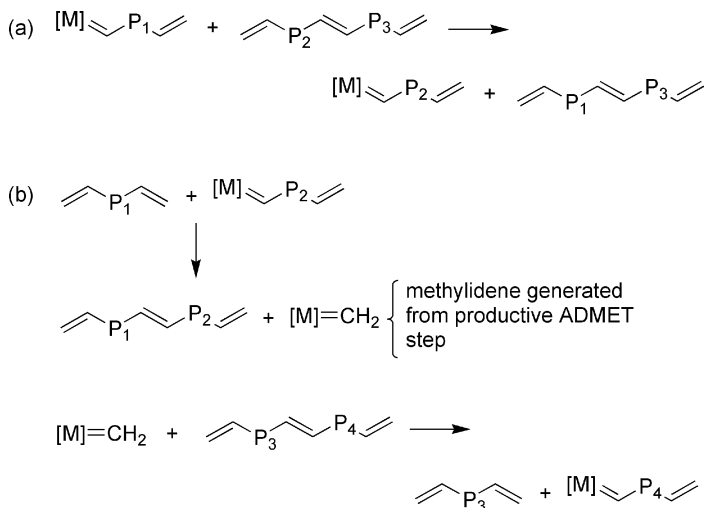
The polydispersity index (PDI) for a polymer is defined as the weight average molecular weight, M_w divided by the number average molecular weight, M_n , and has great impact on the mechanical properties and processability of polymers [74]. Qualitatively, the PDI is a measure of the breadth of the molecular weight distribution of a polymer – the higher the PDI, the broader the molecular weight distribution. Polydispersity indices greater than 1.0 are generally preferred from a materials processing standpoint. The statistical treatment of condensation polymerizations predicts that the PDI will approach 2.0 as the conversion approaches 100%, according to Eq. (2). In fact, a PDI of approximately 2.0 is observed for most ADMET polymerizations. The kinetics of chain polymerization is more complicated. Due to various effects, the PDI of polymers produced by chain polymerization can range from 1 to 40 or higher. Indeed, living ROMP can produce polymers with PDI approaching 1.0, whereas traditional ROMP polymers often have higher values of PDI. Many ROMP polymers display PDI of 1.1–1.7. If another mechanism were in place, such as RCM of an ADMET monomer followed by ROMP of the cyclic olefin thus formed, the observed PDI would be expected to vary from the value of 2.0, depending on the monomer used and the kinetics of the process.

3.9.2.3

Interchange Reactions

Interchange reactions occur if the functional groups of a polymer chain are still active towards the condensation reaction and can undergo reaction with the end groups of the polymer. For example, the backbone ester groups of a polyester can undergo reaction with an alcohol end group of another polymer chain to produce a new backbone ester bond and a new alcohol end group. These reactions are common in polycondensation and are degenerate in the sense that they do not alter the average molecular weight of the polymer. In the case of ADMET, the carbon-carbon double bonds of the polymer backbone are still active towards olefin metathesis reactions and can undergo reaction with either the metal methylidene or a polymeric metal alkylidene, neither of which affects the average molecular weight of the polymer (Scheme 3.9-6).

Reaction of the metal methylidene with a backbone double bond would appear to reduce the molecular weight of the polymer, but this is the case only if the metal methylidene originated from ethylene rather than from a productive metathesis step. Thus, the overall sequence as shown in Scheme 3.9-6 is degenerate: reaction of a metal alkylidene with an olefin end group to produce a backbone olefin and



Scheme 3.9-6. Metathesis interchange reactions in ADMET polymerization. (a) Interchange reaction of a polymer chain with a metal alkylidene. (b) Interchange reaction of two polymer chains via a metal methyldene.

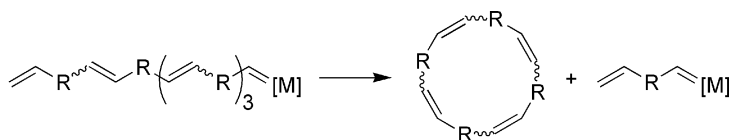
the metal methyldene followed by reaction of this metal methyldene with a backbone double bond to produce a polymeric metal alkylidene and an olefin end group.

Although the presence of interchange reactions in a typical ADMET polymerization leads to no change in the average molecular weight of the polymer, these reactions allow ADMET depolymerization with ethylene or other olefins (see Section 3.9.8). Interchange reactions also allow the random incorporation of an ADMET monomer into a different unsaturated ADMET homopolymer to form a random copolymer of the two monomers [75]. By comparison, the double bonds of some ROMP polymers, such as polynorbornene, are sterically hindered and thus undergo these interchange reactions sluggishly or not at all [76].

3.9.2.4

Cyclization vs. Polymerization

It is well known that an equilibrium exists between cyclic and linear oligomers and polymers in polycondensation chemistry [77]. Cyclics are formed by intramolecular “backbiting” of an oligomeric or polymeric metal carbene with a backbone double bond of the same chain. Generally, high monomer concentration will favor polymerization and linear chain extension over cyclization, since high concentration favors intermolecular over intramolecular reactions. Oligomeric cyclics have been observed in ADMET polymerization [78] and ROMP [79]. Normally, cyclics are not expected for chain polymerization, such as the free-radical polymerization of styrene, but ring-opening polymerization is an exception. ROMP cyclics form by



Scheme 3.9-7. Formation of cyclics in ADMET and ROMP.

the same mechanism as ADMET cyclics, namely, backbiting of one of the backbone double bonds of the same chain (Scheme 3.9-7). This phenomenon has recently been exploited in the synthesis of wholly cyclic ROMP polymers by an interesting modification of complex **[Ru]2** [80].

Acyclic diene metathesis takes this concept a step further in that the monomers for ADMET are theoretically capable of cyclizing unimolecularly by the RCM reaction. Thus, monomers that will cyclize to a 5-, 6-, or 7-membered ring should be avoided if possible in ADMET. RCM is so competitive that exposing 1,7-octadiene to various metathesis catalysts gives quantitative yield of cyclohexene, despite high concentration of diene. Monomers that would hypothetically cyclize to give 3- and 4-membered rings or larger than a 7-membered ring reliably favor polymerization over cyclization in ADMET conditions (concentrated solutions). However, RCM is capable of synthesizing rings of more than 20 atoms under the proper conditions (high dilution) [81].

3.9.2.5

Monomer Purity

One final aspect of ADMET chemistry related to the condensation polymerization mechanism is that monomers for ADMET polymerization must be pure for two reasons. First, any monofunctional olefins that are present will act as end-capping reagents and will limit the molecular weight of the polymer. For example, in the case of 1,9-decadiene containing 1-decene as an impurity, the number-average degree of polymerization, \bar{X}_n , will vary with the amount of 1-decene according to Eq. (2), where p is the conversion of the functional groups and F_{MO} is the mole fraction of 1-decene in the monomer feed (Figure 3.9-2).

$$\bar{X}_n = \frac{1}{(1 - p + pF_{MO})} \quad (2)$$

Furthermore, for any polycondensation, the conditions employed to effect the polymerization must be such that the condensation reaction is not accompanied by any side reactions. In the context of ADMET, cationic addition to the olefin is the most commonly encountered side reaction, mainly for the classical catalyst systems. Fortunately, modern, well-defined olefin metathesis catalysts tend to be very chemoselective for olefin metathesis and the conditions employed for metathesis reactions are quite mild.

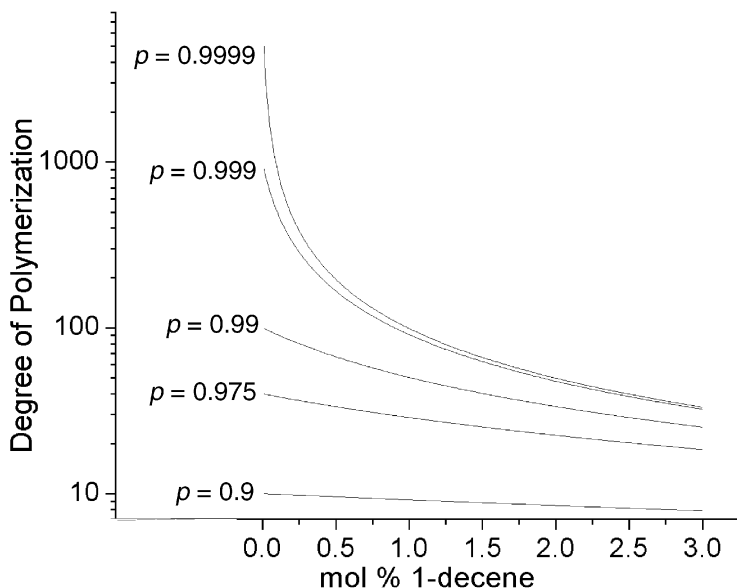


Fig. 3.9-2. Theoretical graph of the degree of polymerization vs. mole% monoolefin for the polymerization of 1,9-decadiene with 1-decene as impurity.

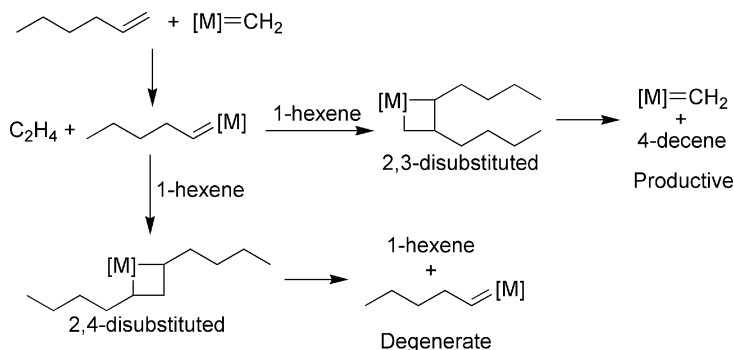
3.9.3

Early Observations in the Evolution of ADMET Polymerization: Reactions of Non-Conjugated Dienes with Classical Metathesis Catalysts

Many of the classical catalysts metathesize internal olefins more rapidly than external olefins, presumably due to the more favorable electronics of interaction of high oxidation metals with electron-rich internal olefins as compared to mono-substituted external olefins [82]. Furthermore, degenerate metathesis was predicted to be the dominant regiochemical course of metathesis of terminal olefins, because the α,α' -disubstituted metallacyclobutane intermediate was thought to be vastly favored over the α,β -disubstituted metallacyclobutane due to steric crowding in the latter (Scheme 3.9-8).

Thus, with many exceptions, dimerizations of terminal olefins often produced less than quantitative yields of products [82], yields that in some cases could be increased by removal of ethylene from the reaction. Additionally, classical catalyst mixtures often promoted olefin isomerization concurrently with metathesis to give complex mixtures of products. For these reasons, metathesis polymerization seemed to be restricted to the chain polymerization ROMP.

Nevertheless, there were several reports of the metathesis of non-conjugated dienes using classical catalysts to yield oligomeric products. Exposure of 1,4-pentadiene with $\text{Bu}_4\text{N}[\text{MoCl}(\text{CO})_5]/\text{MeAlCl}_2$ produced the metathesis dimer, 1,4,7-octatriene, in 70% yield [83]. 1,5-Hexadiene in the presence of $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3/$



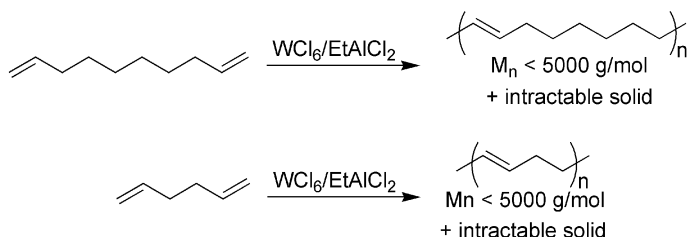
Scheme 3.9-8. Dimerization of external olefins vs. degenerate metathesis.

CsNO_3 generated oligomers up to the pentamer [84] and in the presence of $\text{WCl}_6/\text{Me}_4\text{Sn}/\text{PrOAc}$ with a monoolefin end-capping reagent to give polymer with a DP of up to 55 [85]. The fact that these attempts did not produce high polymer is explained by examination of Figure 3.9-1. Conversions with terminal olefins using these classical catalysts are not extremely high, typically 85–90% in the best cases, such that high polymer is not predicted from the Carothers equation.

Dienes able to cyclize to low-strain cycloolefins were observed to do so when subjected to classical olefin metathesis catalysts. This is quite an important result in terms of ADMET polymerization in that the intermolecular version of ADMET (now known as RCM) is always possible, as discussed in Section 3.9.2.4. Reactions of the $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3/\text{CsNO}_3$ catalyst system with various dienes performed by Kawai and coworkers illustrate quite well the trend of forming cyclics versus linear products [84]. These results are summarized in Table 3.9-1. The trend to cyclize correlates with the degree of strain in the cycloolefin resulting from RCM; the lower the strain of the cyclic olefin that would be formed from RCM, the greater the propensity of the diene to cyclize rather than polymerize. Internal hydrocarbon dienes also were observed to readily cyclize; for instance, *cis,cis*-2,8-decadiene cyclizes to cyclohexene in the presence of $\text{MoCl}_2(\text{PPh}_3)_2(\text{NO})_2/\text{Me}_3\text{Al}_2\text{Cl}_3$ [86] or $\text{MoO}_3/\text{CoO}/\text{Al}_2\text{O}_3$ [87]. Additionally, 1,4-hexadiene and 1,4-octadiene both were observed to yield 1,4-cyclohexadiene, a cyclic “dimer,” when subjected to $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3/\text{CsNO}_3$ [84]. The cyclization trend does not extend past the medium-sized

Tab. 3.9-1. Formation of cyclic olefins vs. linear olefins for reaction of hydrocarbon dienes with $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3/\text{CsNO}_3$ [84].

<i>Diene</i>	<i>Cyclic product</i>	<i>Yield cyclic</i>	<i>Yield dimer</i>	<i>Yield trimer</i>
1,6-heptadiene	Cyclopentene	85	7	1
1,7-octadiene	Cyclohexene	100		
1,8-nonadiene	Cycloheptene	30	48	15
1,9-decadiene	Cyclooctene	Trace	75	

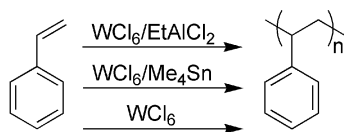


Scheme 3.9-9. ADMET of 1,9-decadiene and 1,5-hexadiene with a classical catalyst mixture.

rings, however; large rings with little strain are not formed in concentrated solution, presumably due to the entropic barrier to cyclization of this type versus intermolecular reaction to produce linear polymer. For example, 1,13-tetradecadiene was observed to give only the linear “dimer” (no cyclization) when subjected to the $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ catalyst system [88].

Wagener and coworkers reinitiated the study of condensation metathesis of unconjugated α,ω -dienes in the late 1980s with reactions of 1,9-decadiene and 1,5-hexadiene with the $\text{WCl}_6/\text{EtAlCl}_2$ catalyst system (Scheme 3.9-9) [89]. The reaction of this catalyst mixture with 1,9-decadiene was fast as judged by rapid evolution of a gas, which was trapped at low temperature and found to be mostly ethylene. The reaction produced soluble viscous oil and intractable solid. The soluble oil was found to be identical with oligomeric polyoctenamer, having an average M_n of less than 5000 g mol^{-1} . The rate of the polymerization of 1,5-hexadiene was slower than that of 1,9-decadiene, as judged by the rate of gas evolution. However, if a slight vacuum was applied to the system, gas was vigorously evolved and the soluble fraction of the product was found to be identical with 1,4-polybutadiene.

Although the insoluble products of these polymerizations were not rigorously characterizable, they were found by ^1H NMR to contain aliphatic CH groups. Both cationic vinyl addition chemistry and addition of organoaluminum compounds to carbon-carbon double bonds were well known to be side reactions for some metathesis reactions with classical catalysts [90]. Assuming that the intractable solid is cross-linked, cationic vinyl addition seems plausible as the source of this material, since addition of an olefin of one polymer chain to an olefin of another chain would lead to a cross-linked polymer. This assumption is supported by the reaction of the $\text{WCl}_6/\text{EtAlCl}_2$ catalyst system with styrene, a compound that is suitable for cationic polymerization due to the stabilization of the propagating benzylic carbocation [89]. This reaction produced exclusively polystyrene, presumably by cationic polymerization. Polystyrene also was produced if tetramethyltin was used as co-catalyst, and indeed even if WCl_6 alone was reacted with styrene (Scheme 3.9-10). Vinyl addition competes with olefin metathesis using this particular classical catalyst system, due to the Lewis acidic nature of the components of the catalyst mixture. There have been several examples of ADMET polymerization using classical catalyst mixtures with fewer Lewis acidic components or added Lewis bases since these findings [91–93], but the use of classical catalyst mixtures for ADMET has



Scheme 3.9-10. Vinyl addition of styrene with classical catalyst mixtures and WCl_6 . No metathesis occurs.

been made mostly obsolete by the success of ADMET with well-defined metathesis catalysts.

Fortunately, Schrock and coworkers were creating Lewis-acid-free metathesis catalysts at the time this work was begun [48]. These complexes required no co-catalysts and the metal was expected to be less Lewis acidic than WCl_6 due to the ancillary ligands. The realization that vinyl addition was a competing mechanism with ill-defined catalysts, combined with the advent of Schrock's well-defined catalyst, made ADMET a reality in terms of formation of high polymer.

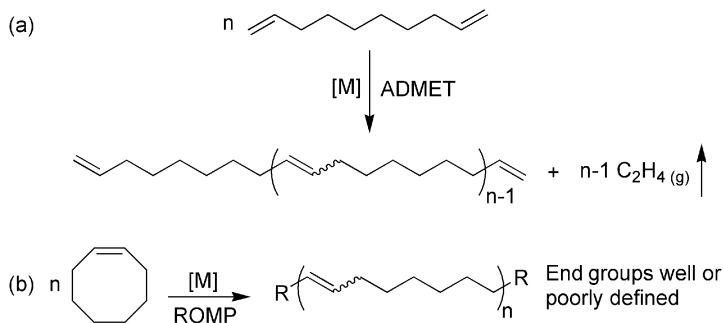
3.9.4

ADMET of Non-Conjugated Hydrocarbon Dienes with Well-Defined Metathesis Catalysts

3.9.4.1

Linear Terminal Dienes

1,9-Decadiene The benchmark reaction to test the applicability of various metathesis catalysts for ADMET polymerization is the polymerization of 1,9-decadiene (Scheme 3.9-11). This monomer is not apt to cyclize in concentrated solution and the product, polyoctenamer, is well known, easily isolated, and easily characterized. 1,9-Decadiene was successfully polymerized with catalysts [W]1 and [W]2 to give polyoctenamer in a variety of molecular weights, up to M_n of 57,000 g mol^{-1} and M_w of 108,000 g mol^{-1} , depending on conditions employed [94]. These polymers had a PDI of 1.9–2.1, which is consistent with the polycondensation mechanism



Scheme 3.9-11. (a) ADMET polymerization of 1,9-decadiene. (b) ROMP of cyclooctene.

for ADMET. Procedurally, monomer and catalyst were combined using break-seal techniques and polymerized under vacuum in toluene solution. These polymers had *trans* contents of between 77–93%, which is quite different from that of the commercially available polyoctenamer produced by ROMP of cyclooctene with classical catalysts, which have *trans* contents of between 60–80% [95]. The higher *trans* content of ADMET polyoctenamer versus the commercial ROMP polymer is due to secondary metathesis reactions of the catalyst with the backbone double bonds of the polymer. Many classical ROMP catalysts are active only for strained olefins, and hence secondary metathesis reactions with the backbone double bonds occur to a much lesser extent, which prevents equilibration of the stereochemistry of the backbone olefins. Thus, ADMET polyoctenamer made with [W]1 generates a thermodynamically controlled ratio of *trans/cis* olefins by repeated secondary metathesis reactions (interchange reactions), whereas classical ROMP catalysts that are active only towards strained olefins give polyoctenamer with a kinetically controlled olefin stereochemistry.

The melting points (T_m) of these highly *trans* polyoctenamer samples are higher than those of the commercially available polymers; for example, the melting point of polyoctenamer with 92% *trans* content was 68 °C, which was more than 15 °C higher than any other polyoctenamer reported at the time. The variation of T_m with *trans* content of the polymer is well behaved and predicts the T_m of purely *trans* polyoctenamer to be 77 ± 1 °C (Table 3.9-2).

^{13}C NMR analysis of oligomeric polyoctenamer demonstrated that the end groups for these polymers were well-defined terminal olefins. The number-average molecular weight for oligomeric ADMET polyoctenamer established by ^{13}C NMR end-group analysis was in good agreement with that obtained by size-exclusion chromatography (11,000 and 12,000 g mol⁻¹, respectively).

A sufficient ratio of monomer:catalyst for the polymerization of non-conjugated hydrocarbon monomers with [W]1 and [W]2 is typically 1000:1, although in many cases ADMET is successful with even less catalyst than that. The polymerization of 1,9-decadiene using [Mo]2 produces results similar to those with [W]1 and [W]2, although the rate is much faster, probably by a factor of 10 based on the time required for crystallization of the oligomer [96]. This observation was consistent

Tab. 3.9-2. Variation of T_m with *trans* content of polyoctenamer.

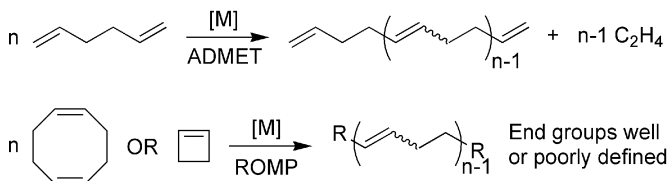
% <i>trans</i>	T_m (°C)	T_c (°C)
77	52.0	31.6
80	55.7	36.8
85	57.1	41.7
88	63.5	44.2
90	66.3	52.3
91	67.6	54.1
93	69.2	56.8

with the observation by Schrock et al. that the molybdenum complexes are more active towards terminal double bonds than are the analogous tungsten complexes [52].

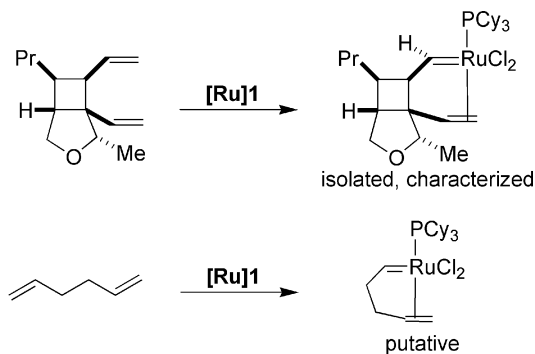
On the other hand, marked differences were observed in the polymerization of 1,9-decadiene with **[Ru]1** [97]. Polymerization of 1,9-decadiene with **[Ru]1** at a monomer:catalyst ratio of 1000:1 produced polyoctenamer with M_n of only about 3700 g mol⁻¹. The PDI was 2.3, and the stereochemistry was 80% *trans*. However, at a monomer:catalyst ratio of 400:1, polyoctenamer with a molecular weight of 20,000–30,000 g mol⁻¹ can be produced. This is typical of the maximum molecular weight that can be achieved with catalyst **[Ru]1**, although this complex is much easier to handle and is more functional group tolerant than the early-transition metal metathesis catalysts. Lower molecular weight is simply a reflection of the conversion possible with the two catalysts.

Polymerization of 1,9-decadiene with **[Ru]2** under the standard ADMET conditions produces a less-well-defined polymer with a lower melting point than polyoctenamer, albeit at a higher molecular weight, than that obtained by polymerization of 1,9-decadiene with catalyst **[Ru]1** [98]. The ¹³C NMR displays the signals expected for polyoctenamer and a number of small signals, which had never been previously observed for the ADMET of 1,9-decadiene. A model study of the reaction of catalyst with 1-octene, 2-nonene, and 7-tetradecene showed that this catalyst readily promotes migration of olefins on a timescale similar to that of metathesis under the standard ADMET conditions of about 60 °C and high concentration of olefin [99]. This study is consistent with other observations of olefin isomerization in the context of RCM [81, 100, 101]. More recently, it has been observed that low temperatures (0 °C) and careful catalyst selection are useful in enhancing the selectivity of this highly useful class of catalysts [102].

1,5-Hexadiene The ADMET polymerization of 1,5-hexadiene with **[W]1** produces polybutadiene in the 1,4 mode exclusively [94], as does the ROMP of cyclobutene [103–106] or 1,5-cyclooctadiene (Scheme 3.9-12) [107–109]. ADMET polybutadiene has a *trans* content of 75%, which is close to the thermodynamically predicted stereochemistry [110] for this polymer and is higher than that of 1,4-polybutadiene produced by ROMP. The polymer is produced with a number-average molecular weight of approximately 8000 g mol⁻¹ and polydispersity near 2.0. The end groups are well-defined terminal alkenes, and these results were similar to those obtained with the use of the molybdenum catalyst **[Mo]2**.



Scheme 3.9-12. (a) ADMET polymerization of 1,5-hexadiene.
(b) ROMP of 1,5-cyclooctadiene or cyclobutene.



Scheme 3.9-13. Reaction of 1,5-dienes with **[Ru]1**.

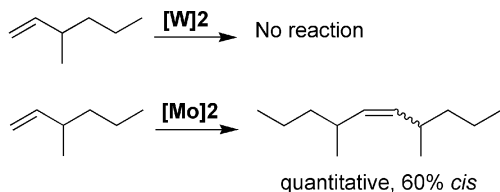
In contrast to the results above, ADMET polymerization of 1,5-hexadiene with **[Ru]1** produces an oligomer with M_n of only 1000 g mol^{-1} [97]. Cyclics, especially 1,5-cyclooctadiene, are produced and unreacted monomer is also present after long reaction times. These results are obtained even with the relatively high monomer:catalyst ratio of 400:1. Stable intramolecular coordination of the distal olefin of the 4-penten-1-ylidene complex to the metal center could occur and obstruct bimolecular coordination of another diene molecule to the metal center, thus preventing further polymerization. One such olefin chelate of a highly substituted 1,5-diene has been isolated and characterized by Snapper and coworkers (Scheme 3.9-13) [111]. This complex was active towards ROMP, but the initiation rate of the catalyst for ROMP of cyclooctene was approximately four times slower than that with **[Ru]1**, which is consistent with a relatively strong interaction between the olefin and the ruthenium atom. The lack of this effect in Schrock's catalyst is at least in part due to the steric congestion about the metal center and the lack of a labile ligand. The polymerization of 1,5-hexadiene with the second-generation ruthenium catalysts has yet to be investigated.

3.9.4.2

Branched Terminal Dienes

Given the success of ADMET polymerization of 1,9-decadiene and 1,5-hexadiene, the scope and limitations of this polymerization were investigated in detail. Branched hydrocarbons were studied in order to determine the effect of steric interactions in the vicinity of the polymerizable double bond. Model compound studies were useful to determine the limitations of the polymerization and to explain the observations. A number of these observations are described below.

3-Methyl 1,4-pentadiene, which would be expected to undergo dimerization/cyclization to 3,6-dimethyl-1,4-cyclohexadiene, is inert to **[W]2** [112]. Intramolecular interaction of the distal double bond of the carbene derived by alkylidene exchange of the catalyst with substrate could stabilize the catalyst to such a degree that it is rendered inactive towards further metathesis. To separate this possibility from the steric effect of the allylic methyl group, the reactivity of 3-methyl-1-hexene

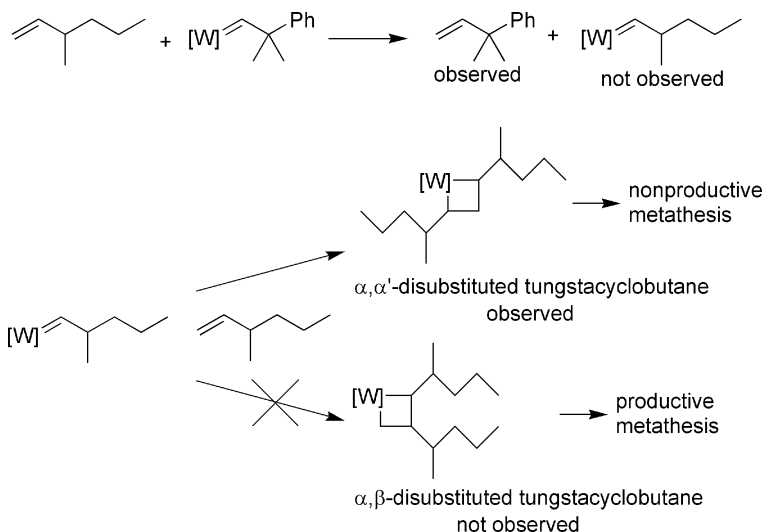


Scheme 3.9-14. Reaction of 3-methyl-1-hexene with **[W]2** and **[Mo]2**.

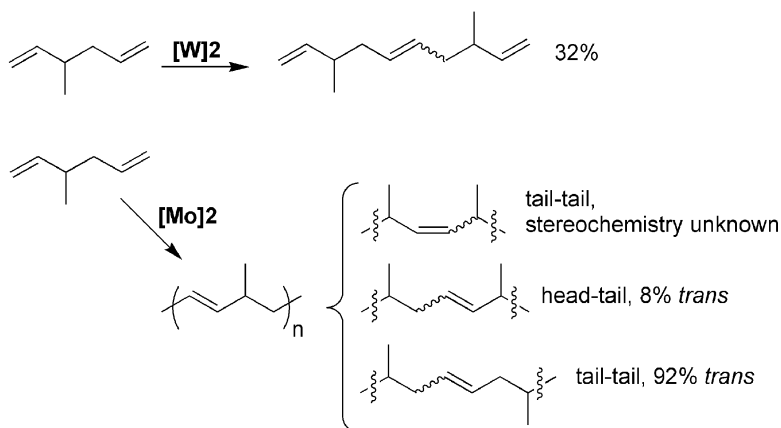
was explored (Scheme 3.9-14). This olefin undergoes no reaction with **[W]2** [113], but quantitative dimerization is observed with **[Mo]2**, which demonstrates the higher activity of **[Mo]2** compared to **[W]2** towards terminal olefins.

NMR analysis gave insight into the inactivity of **[W]2** with 3-methyl-1-hexene (Scheme 3.9-15) [114]. The initial proton signals of the neophylidene carbene were observed to disappear upon addition of 3-methyl-1-hexene to the tungsten complex, and no new alkylidene signals were detected. However, two β -protons of the resulting tungstacyclobutane were observed at 2.5–3.2 ppm, which is consistent with the formation of the α,α' -disubstituted tungstacyclobutane. The exclusive formation of this tungstacyclobutane could be due to prohibitive steric interactions that would be present in the α,β -disubstituted tungstacyclobutane, superior electronic stabilization of the electrophilic metal atom by the α,α' -disubstituted tungstacyclobutane, and/or a restricted orientation of approach of the substrate olefin to the metal carbene.

Furthermore, the chemical shift of the β -protons indicates that the observed tungstacyclobutane is of square planar geometry. Schrock et al. demonstrated that these tungstacyclobutane complexes exist in two geometries that interconvert: square planar and trigonal bipyramidal [49]. The decomposition of tung-



Scheme 3.9-15. NMR evidence related to metathesis of 3-methyl-1-hexene with **[W]2**.



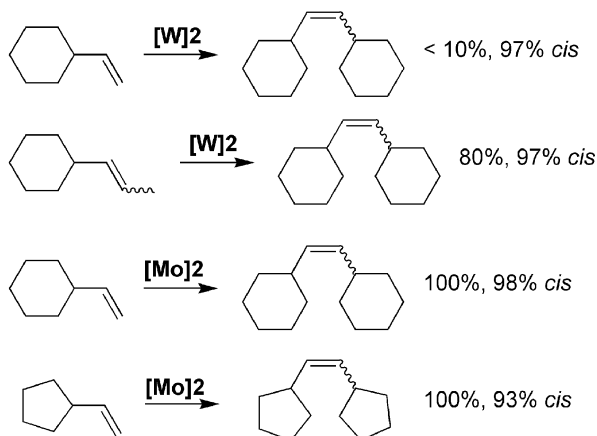
Scheme 3.9-16. Dimerization vs. polymerization of 3-methyl-1,5-hexadiene.

stacyclobutane complexes to olefin and carbene complex proceeds through the trigonal bipyramidal form. The lack of NMR evidence for this form of the tungstacyclobutane indicates that the stability of the square planar α,α' -disubstituted tungstacyclobutane is such that it does not undergo any metathesis, including degenerate metathesis, once it is formed.

3-Methyl-1,5-hexadiene possesses both a double bond with an allylic methyl substituent and a double bond with a homoallylic methyl substituent. Reaction of this diene with $[W]2$ produces the symmetrical dimer corresponding to reaction only at the double bond with the homoallylic substituent in only 32% yield (Scheme 3.9-16) [113]. Attempts to increase the yield of the dimer failed, presumably due to formation of the stable square planar α,α' -disubstituted tungstacyclobutane complex analogous to the one discussed above. Formation of this stable tungstacyclobutane complex would prevent further metathesis of the substrate by consuming the active catalyst.

Molybdacyclobutane complexes are not as stable as the corresponding tungstacyclobutane complexes [52] because the metal-carbon bonds of molybdacyclobutanes are shorter than those of the tungstacyclobutanes, and thus the substituents of the molybdacyclobutanes experience more steric interactions with the other ligands. Tungsten is also more electrophilic than molybdenum and therefore is less likely to eject an olefin. The molybdenum methylidene is more stable than the tungsten methylidene for the same reason. These differences in activity of the two metals were further demonstrated by the polymerization of 3-methyl-1,5-hexadiene with $[Mo]2$ to produce poly(3-methylbutylene), whereas only dimerization was promoted by $[W]2$ [113]. This polymer had an irregular backbone sequence. It consisted of 19% each of head-head and tail-tail linkages and 62% head-tail linkages. The tail-tail linkages were 92% *trans*, whereas the head-tail linkages were only 7.8% *trans* (Scheme 3.9-16).

Restricting the conformation of the substituents is an effective means of coaxing the substrate to undergo metathesis, as witnessed by the fact that vinylcyclohexane

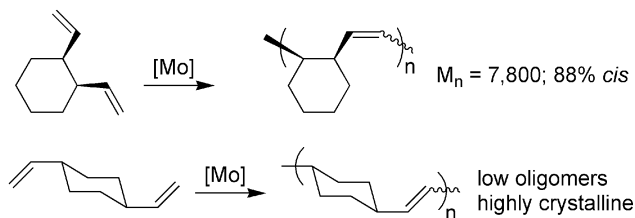


Scheme 3.9-17. Metathesis of vinyl cycloalkanes.

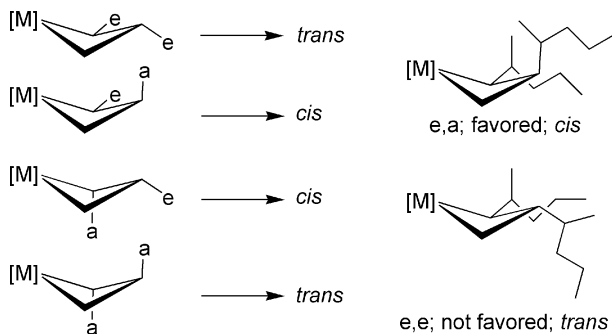
and vinylcyclopentane undergo metathesis dimerization to the corresponding 1,2-disubstituted olefins with $[W]2$ or $[Mo]2$ (Scheme 3.9-17) [114]. Significant amounts of the trigonal bipyramidal tungstacyclobutane were observed by 1H NMR in these experiments; after long reaction times, only the square planar geometry was observed. In accordance with the observation that the tungsten catalysts are more active for internal olefins than for terminal olefins, $[W]2$ is more active towards propenylcyclohexane than towards vinylcyclohexane. This is probably due to the fact that reaction with a 1,2-disubstituted olefin always produces a sterically strained trisubstituted tungstacyclobutane that is apt to decompose into olefin and metal carbene.

Catalyst $[Mo]2$ gives a quantitative yield of dimer from vinyl cyclohexane. This high conversion was extended to the successful polymerization of 1,2-divinylcyclohexane to the corresponding ADMET polymer with M_n of 7800 g mol^{-1} , with PDI of 1.9, and with 88% *cis* content (Scheme 3.9-18) [114]. 1,4-Divinylcyclohexene was also polymerized to a low-molecular-weight, highly crystalline, and mostly insoluble mixture of oligomers.

The stereochemistry of the products of metathesis of substrates with allylic substituents is overwhelmingly *cis*. In the case of the vinylcyclopentane and vinylcyclohexane with catalyst $[Mo]2$, *cis* contents of 93% and 98% were observed. This



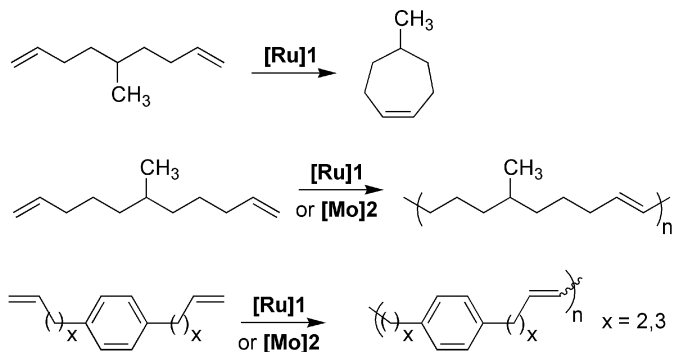
Scheme 3.9-18. ADMET polymerization of divinylcyclohexanes.



Scheme 3.9-19. Conformations of metallacyclobutanes determine stereochemistry of products. a = axial substituent, e = equatorial substituent.

can be explained by a preference for the α -equatorial, β -axial conformation of the metallacyclobutane intermediate in these cases (Scheme 3.9-19) [114]. Normally, the equatorial, equatorial conformation is favored, which leads to *trans* olefins. An α -axial substituent on the metallacyclobutane is strongly disfavored due to steric interactions with the ancillary ligands of the complex, which leads to the assumption that the α -equatorial, β -axial conformation is responsible for the stereochemistry of these reactions.

If at least two methylene units separate the branch point and the olefin, there is little effect on the catalysis. Thus, a series of methyl-substituted polymers has been synthesized with [Mo]2 and [Ru]1 (see Section 3.9.11) (Scheme 3.9-20). Hydrocarbon dienes containing aromatic groups are also readily polymerizable by ADMET with all of the well-defined catalysts, even if there is only one methylene group separating the olefin and the aromatic group. A series of poly(1,4-alkylenephénylene)s has been prepared by ADMET with [Mo]2, [Ru]1, and classical catalyst mixtures [115]. Catalyst choice is dependent on the number of carbons separating the phenylene moieties.



Scheme 3.9-20. ADMET polymerization of branched and aromatic hydrocarbon monomers.

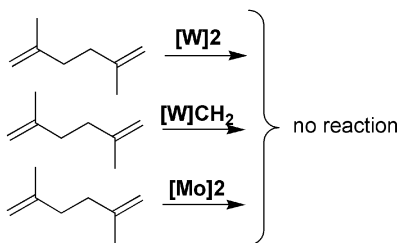
The ultimate outcome of these observations in relation to ADMET polymerization is that allylic-substituted dienes are not polymerizable with Schrock's tungsten catalysts but are somewhat polymerizable with the molybdenum complex **[Mo]2**. The molecular weight of the polymer obtained from 3-methyl-1,5-hexadiene was low, indicating that the conversion was less than that obtained with unbranched dienes. Consequently, the vast majority of ADMET polymerizations have been conducted on terminal dienes with no branching within three carbons of the olefin to give polymers with predominantly *trans* backbone olefins.

3.9.4.3

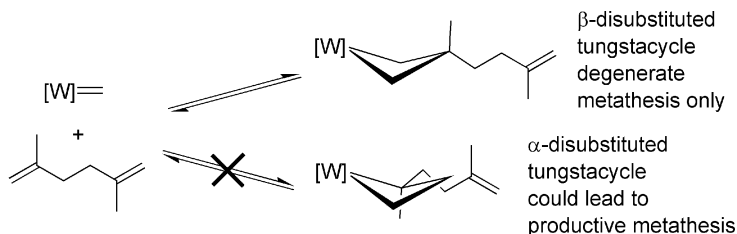
Geminal Disubstituted Olefins

The ADMET reactivity of geminal disubstituted olefins with Schrock's catalysts was investigated in detail. 2,5-Dimethyl-1,5-hexadiene was exposed to catalysts **[W]2** and **[Mo]2**, and only monomer was recovered from each experiment (Scheme 3.9-21) [113]; ^1H NMR showed that no exchange of the geminal disubstituted olefin occurred with the neophylidene-carbene complexes of either metal. Conversion of the neophylidene complex **[W]2** to the corresponding tungsten-methylidene complex by reaction of **[W]2** with ethylene and subsequent exposure of this complex to 2,5-dimethyl-1,5-hexadiene also showed no sign of reaction. This indicates that the geminal disubstituted double bond is inert to **[W]2** in either the pre-catalytic or catalytic forms.

Reaction of a diene possessing both a geminal disubstituted olefin and a monosubstituted olefin yielded different results, however. With **[W]2**, 2-methyl-1,5-hexadiene underwent metathesis only at the monosubstituted double bond to produce the dimer, 2,9-dimethyl-1,5,9-decatriene [113]. Although the condensation reaction of the monosubstituted olefins would generate the methylidene complex, no activity was observed for the geminal disubstituted double bond, further demonstrating the complete inertness of this moiety towards the tungsten catalyst. It is also possible that only degenerate metathesis occurs on the geminal disubstituted double bond, which would imply that the disubstituted carbon could occupy only the β -position of the tungstacyclobutane, although a stable tungstacyclobutane was not observed by ^1H NMR (Scheme 3.9-22).



Scheme 3.9-21. Reaction of 2,5-dimethyl-1,5-hexadiene with catalyst **[W]2**, the methylidene analogue of **[W]2** (denoted **[W]CH₂**), and **[Mo]2**.

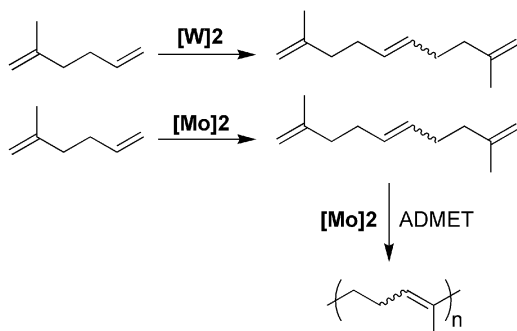


Scheme 3.9-22. Possible outcomes of reaction of methylidene analogue of [W]2 with 2,5-dimethyl-1,5-hexadiene. Neither tungstacyclobutane was observed by ^1H NMR.

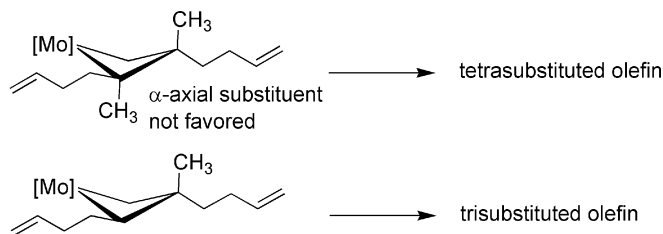
Catalyst [Ru]1 also only dimerizes 2-methyl-1,5-hexadiene at the monosubstituted olefin [97]. The reactivity of this diene with the second-generation ruthenium complexes has not yet been explored, however.

In contrast to the above results, exposure of 2-methyl-1,5-hexadiene to [Mo]2 produced a low-molecular-weight polymer (Scheme 3.9-23). Further analysis revealed that dimerization proceeds initially, followed by slow metathesis of the geminal disubstituted olefins with the 1,2-disubstituted olefins to generate 1,4-polyisoprene with a *Z/E* ratio of 0.53 by ^{13}C NMR. The M_n of the 1,4-polyisoprene was 6800 g mol^{-1} by ^{13}C NMR and 4900 g mol^{-1} by VPO, which is relatively low compared to polymerization of terminal monosubstituted dienes with the same catalyst. The ROMP of 1-methylcyclobutene with $\text{Ph}_2\text{C}=\text{W}(\text{CO})_5$ also produces linear polyisoprene [116], but this polymer is different from ADMET polyisoprene in that the ROMP polymer contained 20% disubstituted and tetrasubstituted double bonds, whereas the ADMET polyisoprene contains no disubstituted or tetrasubstituted double bonds. One possible explanation for this observation is that the geminal disubstituted double bond participates in metathesis only as the β-substituent on the molybdacyclobutane, thus never allowing the formation of tetrasubstituted double bonds (Scheme 3.9-24).

The exocyclic geminal disubstituted olefin methylene cyclohexane also was subjected to ADMET conditions to determine whether restricting the conformation



Scheme 3.9-23. Metathesis of 2-methyl-1,5-hexadiene.



Scheme 3.9-24. $\alpha,\alpha,\beta,\beta$ -Tetrasubstituted molybdacyclobutane would be required for the formation of tetrasubstituted olefins in ADMET polyisoprene.

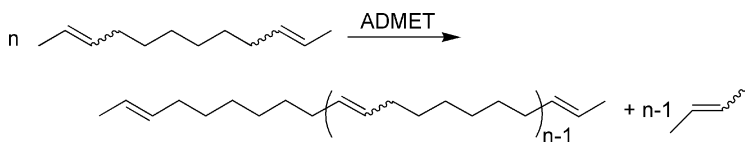
of the substituents of geminal disubstituted double bonds is a viable method of allowing polymerization of 1,1-disubstituted olefins. Complex **[Mo]2** does not undergo any reaction with methylenecyclohexane, as judged by the persistence of the neophylidene signals in ^1H NMR. Catalyst **[W]2** does exchange with the substrate as judged by NMR, but no further productive metathesis occurs. The exchange of the initial carbene with this olefin is also less than quantitative. This result indicates enhanced activity of **[W]2** for the exocyclic double bond compared to the geminal disubstituted double bond of 2-methyl-1,5-hexadiene, but it is not enhanced enough to promote even dimerization of the substrate, let alone ADMET polycondensation.

The conclusion from these experiments is that ADMET of geminal disubstituted olefins is feasible only with **[Mo]2** and olefins in which one of the substituents is no larger than methyl. This selectivity was taken advantage of in the polymerization of 2-methyl-1,5-hexadiene to produce polyisoprene with only 1,4-linkages and entirely in a head-tail arrangement.

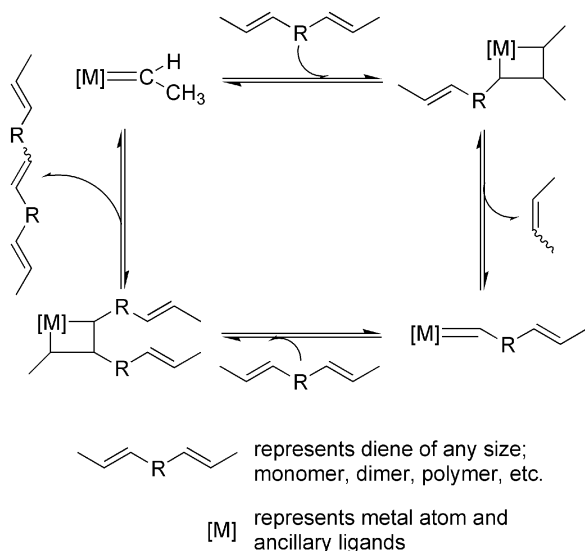
3.9.4.4

1,2-Disubstituted Olefins

ADMET of 1,2-disubstituted olefins with Schrock's catalysts proceeds similarly to that of monosubstituted olefins, but conversions, and hence the achievement of high molecular weight, are not as high as those observed for terminal dienes. For example, 2,10-dodecadiene has been successfully polymerized with catalyst **[Mo]2** to produce polyoctenamer ($M_n \sim 2800 \text{ g mol}^{-1}$) (Scheme 3.9-25) [117]. The lower molecular weight is due to the fact that the condensate molecule, 2-butene, is not



Scheme 3.9-25. ADMET of 2,10-dodecadiene.



Scheme 3.9-26. Catalytic cycle for ADMET of 1,2-disubstituted dienes. Note that the metal methylidene complex is never formed.

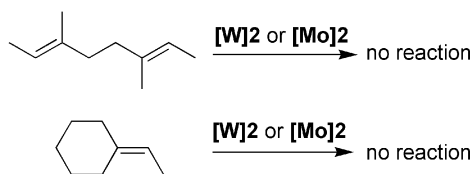
as volatile and easily removed from the reaction as ethylene, and hence the ultimate conversion is lower. Additionally, only trisubstituted molybdacyclobutanes are formed during the ADMET of 1,2-disubstituted dienes, which could limit the conversion by providing a more kinetically difficult reaction sequence.

Monomers of this sort are useful in situations where terminal dienes cannot be employed, such as in ADMET copolymerization with some conjugated monomers [117]. They would also be useful in situations where the methylidene complex must be avoided (Scheme 3.9-26). The methylidene complex of $[\text{Ru}]2$, for example, is particularly unreactive, whereas the corresponding alkylidene complexes are quite reactive due to the kinetics of phosphine dissociation from each [118]. Nonetheless, ADMET polymerization occurs with $[\text{Ru}]2$, and thus rigorous exclusion of the methylidene complex from the catalytic cycle is not necessary for this catalyst, although the need to avoid the formation of the methylidene complex altogether may manifest itself in the future.

3.9.4.5

Trisubstituted Olefins

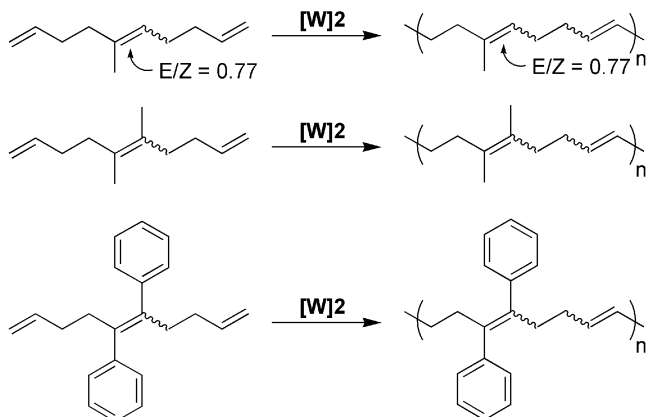
It had been predicted that the olefin metathesis equilibration of the trisubstituted olefin 2-methyl-2-butene is more thermodynamically favorable than that of isobutene, a geminal disubstituted olefin [119]. In order to determine whether this thermodynamic preference would be sufficient to allow ADMET of trisubstituted



Scheme 3.9-27. Attempted metathesis of trisubstituted olefins.

dienes, the model compound 2-methyl-2-butene was subjected to $[W]2$ and $[Mo]2$ in a closed system, and product distributions near the expected thermodynamic distribution were obtained in both cases [113]. However, the attempted ADMET of 3,6-dimethyl-2,6-octadiene, which would give the same polymer as the unsuccessful ADMET polymerization of 2,5-dimethyl-1,5-hexadiene, also failed, as did an attempted ADMET of squalene. In addition, 2-ethylidenecyclohexane also fails to undergo dimerization with catalysts $[W]2$ and $[Mo]2$ (Scheme 3.9-27). These results were interpreted to indicate that trisubstituted double bonds with substituents other than methyl are not metathesizable with Schrock's catalysts, which indicates that ADMET polymerization of any diene with trisubstituted double bonds will not occur.

The fact that the tungsten catalyst does not undergo metathesis with trisubstituted olefins was employed to synthesize several perfectly alternating copolymers of α,ω -dienes possessing internal tri- and tetrasubstituted olefins (Scheme 3.9-28) [120]. These polymers were formed with molecular weights up to approximately $13,000 \text{ g mol}^{-1}$. They are equivalent to perfectly alternating copolymers of butadiene with substituted dienes, both being incorporated only in the 1,4 mode. The lack of participation of the internal double bonds is indicated by the complete preservation of stereochemistry about the internal double bonds and by UV spectroscopy in the case of the stilbene-containing monomers.



Scheme 3.9-28. Polymerization of trienes containing tri- and tetrasubstituted olefins.

3.9.5

ADMET Copolymerization

Copolymerization of different monomers by condensation polymerization is typically a trivial matter. The fact that the polycondensations are carried to very high conversions indicates that the comonomer content in the final polymer will be that of the monomer feed. Comonomers are distributed in a random fashion with a theoretically Bernoullian or first- or second-order Markov distribution [121]. This behavior is in stark contrast to chain polymerization, where differences in the kinetics of chain propagation for different monomers often limit the success of chain copolymerization or restrict the range of comonomer compositions attainable [122]. In the case of ADMET, terminal dienes that have no branching or functionality within three carbons of the olefin are assumed to have approximately equal reactivity towards metathesis condensation. This assumption is supported by the fact that ADMET copolymerization does occur and produces copolymers with a random distribution of the comonomers along the polymer chains.

ADMET copolymerization was definitively demonstrated by the copolymerization of 1,9-decadiene with 1,5-hexadiene [75]. The comonomer content of the copolymers was approximately that of the monomer feed (Table 3.9-3), and detailed ^{13}C NMR analysis confirmed the random nature of the polymer backbone. These copolymers also could be prepared by reaction of one comonomer with the homopolymer of the other comonomer; for example, 1,5-hexadiene can be reacted with polyoctenamer to produce a random copolymer of the two comonomers (Scheme 3.9-29). This observation is proof of the secondary metathesis or interchange reactions that occur on the double bonds of an ADMET polymer backbone. In all cases GPC chromatograms displayed a single peak with the expected distribution and PDI of approximately 2.0.

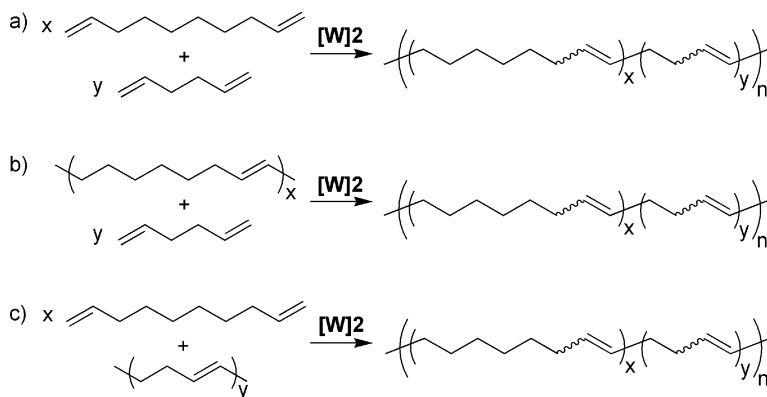
In many cases, monomers that are not capable of ADMET homopolymerization will copolymerize with 1,9-decadiene [78]. Alternatively, monomers that are apt to cyclize will undergo ADMET copolymerization with 1,9-decadiene to linear polymer [78]. ADMET copolymerizations have been successfully performed in a variety of cases. Rather than listing the examples here, examples of ADMET copolymerizations will be given throughout the remainder of the chapter.

ADMET also has been used to prepare graft copolymers. This polymerization

Tab. 3.9-3. Monomer feed ratio vs. copolymer composition for the ADMET copolymerization of 1,9-decadiene and 1,5-hexadiene.

Monomer feed ratio^a	Copolymer composition (octenamer:butadiene)		
	^1H NMR	^{13}C NMR: methylene	^{13}C NMR: alkene
50:50	48:52	51:49	49:51
75:25	72:28	75:25	75:25
95:5	95:5	92:8	92:8

^a Molar ratio of 1,9-decadiene to 1,5-hexadiene.



Scheme 3.9-29. ADMET copolymerization. (a) 1,9-decadiene and 1,5-hexadiene; (b) 1,5-hexadiene and polyoctenamer; (c) 1,9-decadiene and 1,4-polybutadiene.

has the unique ability to precisely control the location of the grafts along the chains. The graft can be polymerized before or after the ADMET reaction. Preparing the macromonomer diene before ADMET polymerization ensures that 100% of the graft sites actually contain grafts, but performing ADMET before installing the grafts usually gives a backbone polymer of higher molecular weight. This strategy has been utilized with living polymerization of ethylene oxide to prepare poly(ethylene oxide) grafts [123] and with atom transfer radical polymerization to prepare grafts of polystyrene or poly(methyl methacrylate) [124].

3.9.6

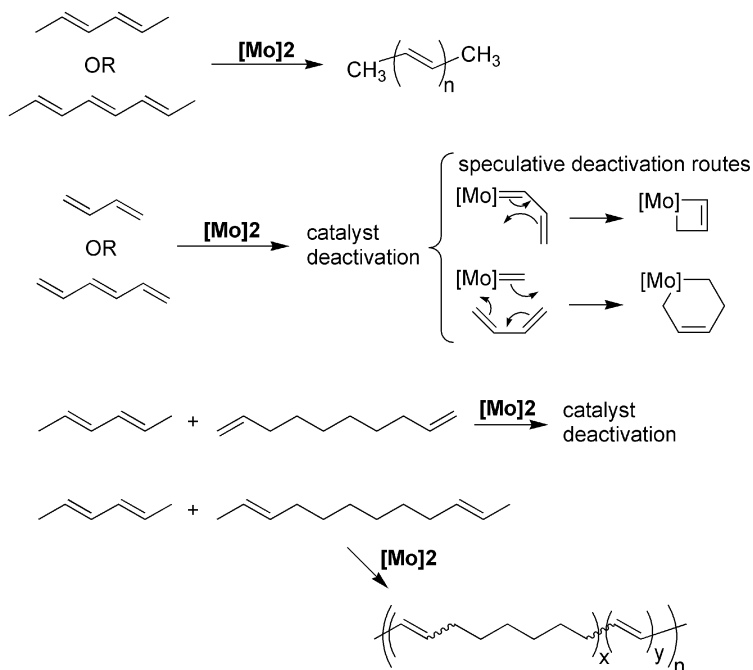
Synthesis of Conjugated Polymers via ADMET

The strong interest in conjugated polymers has spurred investigations of the application of olefin metathesis to the synthesis of conjugated polymers by several research groups. Acetylene polymerization via metathesis and the synthesis of conjugated polymers via ROMP are beyond the scope of this chapter, which will focus on the polycondensation of dienes to give conjugated polymers. Most other methods of conjugated polymer synthesis require harsh conditions or rely on metal-mediated or -catalyzed processes that promote some unwanted side reactions that can alter the photophysical or other target properties of the polymers. However, metathesis preparation of conjugated polymers does not suffer from these drawbacks.

3.9.6.1

Polyacetylenes

Polyacetylene is a well-studied conjugated polymer, and, in fact, the 2000 Nobel Prize in chemistry was awarded for the conversion of polyacetylene to a conductive



Scheme 3.9-30. Polyacetylenes produced by ADMET.

material [125]. Various polyacetylenes may be produced by Ziegler-Natta polymerization of acetylene [126] or by metathesis routes, including ROMP [19]. Oligomeric polyacetylene was successfully produced by ADMET of 2,4-hexadiene by both Schrock's tungsten and molybdenum catalysts (Scheme 3.9-30) [127]. In this case, 2-butene is the condensate molecule. The polymerization may be conducted in bulk or in solution, with the solution method giving higher degrees of polymerization by keeping the system homogeneous at slightly higher conversions. The polyenes formed in bulk had an average degree of polymerization of 6–10, and those polymerized in solution had an average degree of polymerization of 10–15. The end groups of these polymers consisted exclusively of methyl groups. Polyenes are also generated by the polymerization of 2,4,6-octatriene. However, polyenes are not generated by exposure of either 1,3-butadiene or 1,3,5-hexatriene; in fact, reaction of these terminal conjugated olefins with Schrock's catalysts leads to rapid deactivation of the catalysts via an unknown mechanism. Intermolecular reaction of the carbene generated by reaction of the catalysts appears to be responsible for the deactivation via either metallacycle formation or η^3 -allylic coordination (Scheme 3.9-30).

Copolymerization of conjugated monomers and non-conjugated monomers was also successful [127]. Poly(acetylene-*co*-octenamer)s with M_n of about 500–2500 g mol⁻¹, depending on monomer feed ratio, were produced by ADMET of mixtures of 2,4-hexadiene and 2,10-dodecadiene. The polymers were blocky, as

judged by the NMR and UV spectra, with an average of 4 or 5 acetylene units per conjugated block. Copolymerization of 2,5-hexadiene with the terminal diene 1,9-decadiene resulted in catalyst deactivation. This is presumably the same deactivation witnessed in the attempted polymerization of 1,3-butadiene; in this case formation of terminal conjugated units could occur by reaction of the metal methyldene with an internal conjugated unit.

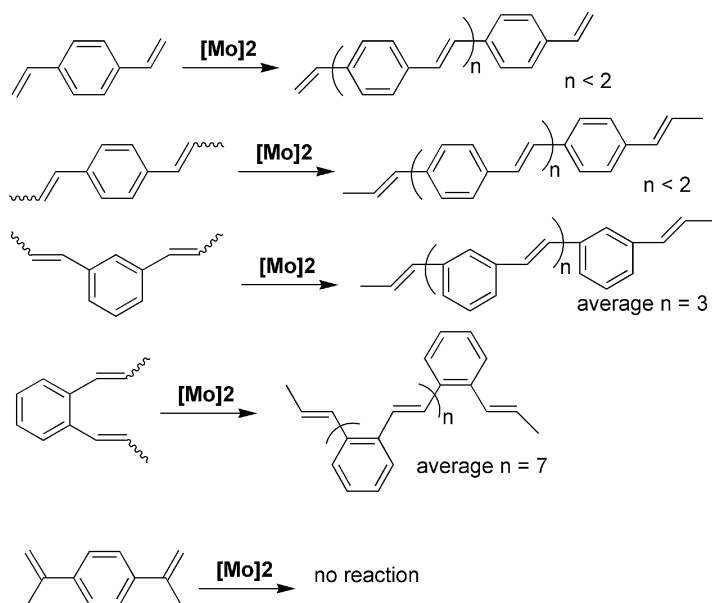
3.9.6.2

Polyphenylenevinylenes

Polyphenylenevinylene (PPV) is another conjugated polymer that has been investigated extensively in relation to its photophysical properties and its use in electronic devices. PPV has been synthesized by several methods, including elimination of a small molecule from a precursor polymer [128–131], the Wittig reaction [132, 133], the Heck reaction [134], ROMP [135–137], and ADMET. The elimination, Wittig, and Heck syntheses of PPV suffer from less than complete reaction under harsh conditions, formation of a relatively high amount of *cis* olefins, and formation of defects such as 1,1-vinylidene groups, respectively, whereas the metathesis routes to PPV are clean, proceed under mild conditions, and produce almost exclusively *trans* vinylene units. The *trans* configuration about the vinylene units is desirable because the *cis* configuration leads to steric interaction between adjacent phenylene moieties. The lack of this steric interaction allows a more planar backbone, which increases the overall effective conjugation length of the polymer. The insolubility and consequent difficult processing of unsubstituted PPV are always a barrier to the synthesis of high-molecular-weight PPV and the successful fabrication of PPV into devices. For these reasons, the soluble precursor routes are typically used in the commercial fabrication PPV-containing devices.

Schrock and coworkers investigated the synthesis of PPV from 1,4-divinylbenzene [138] and found that the degree of polymerization obtained was low. The polymerization of neat 1,4-divinylbenzene has also been investigated with $[\text{Ru}]_2$ [139]. The reaction proceeds rapidly to the dimer, with formation of only small amounts of trimer. Thus, the results obtained seem to be identical despite the catalyst employed, which suggests that the reaction ceases to be productive after the state of matter changes to a solid, although solid-state polymerization remains a possibility for the metathesis preparation of unsubstituted 1,4-PPV.

Wagener and coworkers investigated the polymerization of 1,4-dipropenylbenzene with tungsten catalyst $[\text{W}]_2$ and found that the resultant product consisted mainly of dimer and small amounts of trimer along with monomer [117]. Propenyl benzenes were investigated, since Schrock's catalyst was known to be deactivated towards metathesis with terminal conjugated dienes such as 1,3-butadiene and to avoid uncatalyzed vinyl addition reactions that occur in pure 1,4-divinylbenzene. 1,3-Dipropenylbenzene and 1,2-dipropenylbenzene were polymerized via ADMET (Scheme 3.9-31) [117]. The polymer from 1,2-divinylbenzene had a slightly higher average DP than the other isomers. This monomer polymerized more slowly than the other two isomers, however, and required a greater catalyst loading: 1 equivalent



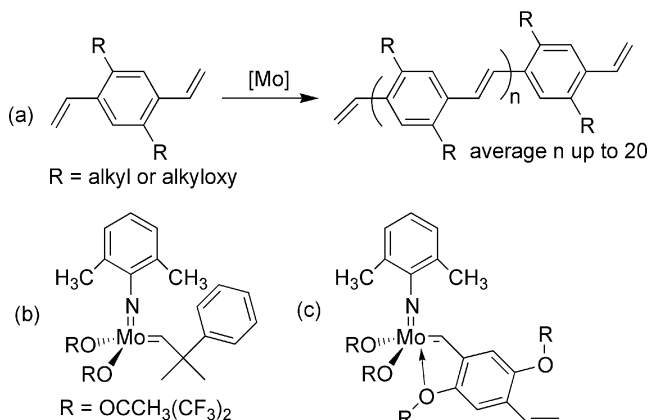
Scheme 3.9-31. PPV via ADMET.

lent of catalyst [Mo]2 per 60 equivalents of monomer. 1,4-Diisopropenylbenzene is inert towards metathesis with catalysts [W]2 and [Mo]2 [113]. High *trans* content was observed in all cases.

1,4-Dipropenylbenzene was successfully copolymerized with 1,9-decadiene [117]. The resulting polymers had only *trans* double bonds connecting phenyl and alkyl groups, contained only methyl end groups corresponding to the placement of the aromatic monomer at the end of the polymer chains, and contained various amounts of aromatic dimer units (4,4'-divinyl-*trans*-stilbenyl moieties) depending on the monomer feed ratio. Somewhat different results were obtained for the copolymerization of 1,2-divinylbenzene with 1,9-decadiene, which gave a random copolymer with only small amounts of adjacent 1,2-phenylenevinylene units. Increasing the amount of 1,2-divinylbenzene in the monomer feed increases the amount of 2,2'-divinyl-*trans*-stilbene units in the polymer. Very similar results were obtained by the polymerization of 1,3-divinylbenzene with 1,9-decadiene.

More recently, a series of relatively high-molecular-weight copolymers of 1,3- and 1,4-divinylbenzene with substituted derivatives has been successfully prepared with complex [Mo]2 and a related complex [140, 141] (Scheme 3.9-32). These polymers all had a very high *trans* content.

Thorn-Csányi and coworkers have synthesized a number of substituted and unsubstituted PPVs by ADMET with [Mo]2 and related complexes (Scheme 3.9-32) [142–145]. Their findings include the fact that molybdenum complexes are more active for this chemistry than the corresponding tungsten complexes, as expected from the other trends for the two metals. Additionally, NMR experiments showed



Scheme 3.9-32. (a) Polymerization of 2,5-disubstituted-1,4-divinylbenzenes. (b) Useful derivative of **[Mo]2** for these ADMET polymerizations. (c) Speculative stable intermediate responsible for slow ADMET kinetics for 2,5-dialkyloxy-1,4-divinylbenzenes.

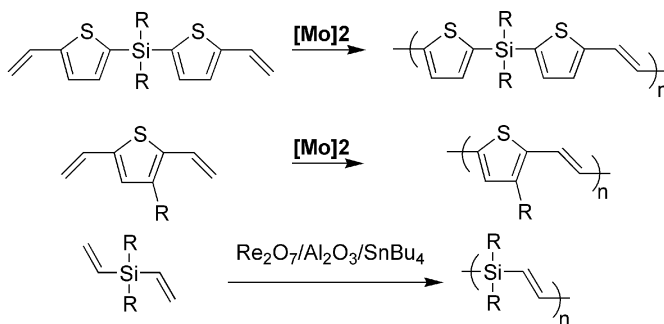
that of the two carbenes involved in the catalytic cycle, methyldiene and benzylidene, benzylidene is by far the more stable in ADMET reactions of this type. A number of 2,5-disubstituted PPVs have been synthesized by ADMET. The substituted PPV achieves slightly higher molecular weight than the unsubstituted monomers, but the chemistry is still restricted to producing oligomers of less than 15 and usually no more than 5 repeat units. In some cases, the derivative of **[Mo]2** shown in Scheme 3.9-32b gives better results than catalyst **[Mo]2** itself, presumably due to the reduced steric encumbrance of the metal to allow for the somewhat bulky substrates to approach and react at the metal center. The kinetics of ADMET polymerization of 2,5-dialkyloxy-1,4-divinylbenzenes is slower than that of 2,5-dialkyl-1,4-divinylbenzenes, presumably due to coordination of the ether oxygen to the metal atom (Scheme 3.9-32c). Such coordination is thought to stabilize the carbene or the metallacyclobutane intermediates and thus to slow the overall reaction. These polymers also display high *trans* double-bond content.

3.9.6.3

Other Conjugated Polymers

Other conjugated polymer backbones have been synthesized via ADMET. 9,9-Dioctyl-2,7-divinylfluorene has been polymerized with catalyst **[Mo]2**, giving a relatively high-molecular-weight polymer [146]. As in other ADMET reactions, high monomer concentrations and reduced pressure were critical to the success of these polymerizations.

Thiophene-containing conjugated polymers have also been prepared by ADMET. Bazan et al. describe the synthesis of low-molecular-weight



Scheme 3.9-33. ADMET polymerization of heteroatom-containing conjugated monomers.

poly[(silanylene)dithienylethylene] derivatives using catalyst **[Mo]2** (Scheme 3.9-33) [147]. Polymerization by vinyl addition was a problematic side reaction in this chemistry, presumably due to the electron-rich heterocycle. Conducting the polymerization in solvent minimized vinyl addition chemistry. 3-Alkyl-2,5-divinylthiophenes have been polymerized with catalyst **[Mo]2** [148]. Vinyl addition reactions were also problematic in bulk polymerization of this monomer, but this could be minimized in solution. The soluble fraction of the solution-polymerized monomer was consistent with poly(alkylthiophenevinylene) with a degree of polymerization of approximately 10.

Kawai and coworkers have achieved ADMET of various divinylsilanes by reaction with the classical catalyst $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3/\text{Bu}_4\text{Sn}$, to produce various σ - π -conjugated oligo(silylene-vinylene)s (Scheme 3.9-33) [149]. Neither Schrock's nor Grubbs well-defined catalysts, nor the WCl_6 - SnBu_4 classical catalyst, is active for the ADMET of these compounds.

Although not as popular as other metal-mediated routes to conjugated polymers, ADMET is a powerful and under-exploited method of synthesizing conjugated polymers. The use of the second-generation ruthenium catalysts to synthesize conjugated polymers has hardly been explored and would not be expected to promote the vinyl addition reactions that have been problematic in ADMET of electron-rich monomers with the more electrophilic molybdenum complexes.

3.9.7

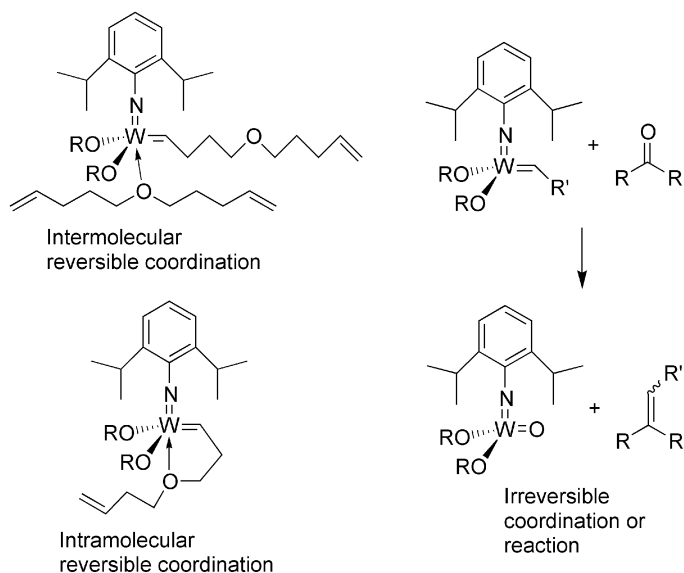
ADMET Polymerization of Functionalized Dienes

The scope of ADMET polymerization covers a wide range of functional groups. The successful polymerization of hydrocarbon dienes with Schrock's catalysts and reports in the literature of high-yielding metathesis reactions with functionalized substrates led to the initial investigations of the applicability of ADMET with functionalized dienes. The main challenge with ADMET of functionalized dienes is that functional group coordination to the metal center can compete with the olefin metathesis reaction. Schrock's catalysts are somewhat electrophilic and thus

potentially are able to interact with electron-rich functional groups. The tungsten complexes are more electrophilic and therefore less tolerant of functional groups than the molybdenum complexes.

The impetus for developing olefin metathesis catalysts of the late-transition metals is to make available less electrophilic complexes that are more tolerant of electron-rich functional groups. There are ill- and well-defined metathesis catalysts of rhenium and ruthenium, for example, to fulfill this need. The ruthenium complexes initially developed by Grubbs and coworkers are especially useful for functionalized dienes that are not tolerated by Schrock's catalysts, although there are examples of functionalized dienes that are better polymerized by Schrock's molybdenum catalyst than by Grubbs catalyst (thioethers, for example). The second-generation ruthenium catalysts are especially useful for ADMET of functionalized substrates and have allowed polymerization of dienes containing multiple amino acid residues [151]. These late-transition metal catalysts are not immune to interaction with functional groups, however, since chelates of functionalized olefins with ruthenium olefin metathesis catalysts have been isolated and characterized [111, 151]; the Hoveyda catalysts are an example of this phenomenon that retains high catalytic activity [67].

Concerning the molecular nature of functional group tolerance, coordination of the electron-rich functional group to the metal is of central focus (Scheme 3.9-34). Reversible coordination to the metal could compete with coordination of the polymerizable olefins, which could simply retard the ADMET reaction or prevent high conversion. If high conversion is not attained, then only oligomers will be formed. The effects of reversible coordination have been quantitatively observed in kinetic



Scheme 3.9-34. Proposed modes of interactions of functional groups with metathesis catalysts.

studies of ADMET polymerization and will be discussed in detail in Section 3.9.10. Reversible coordination could occur intermolecularly or intramolecularly, in which a functional group of the carbene unit coordinates to the metal atom of the same complex.

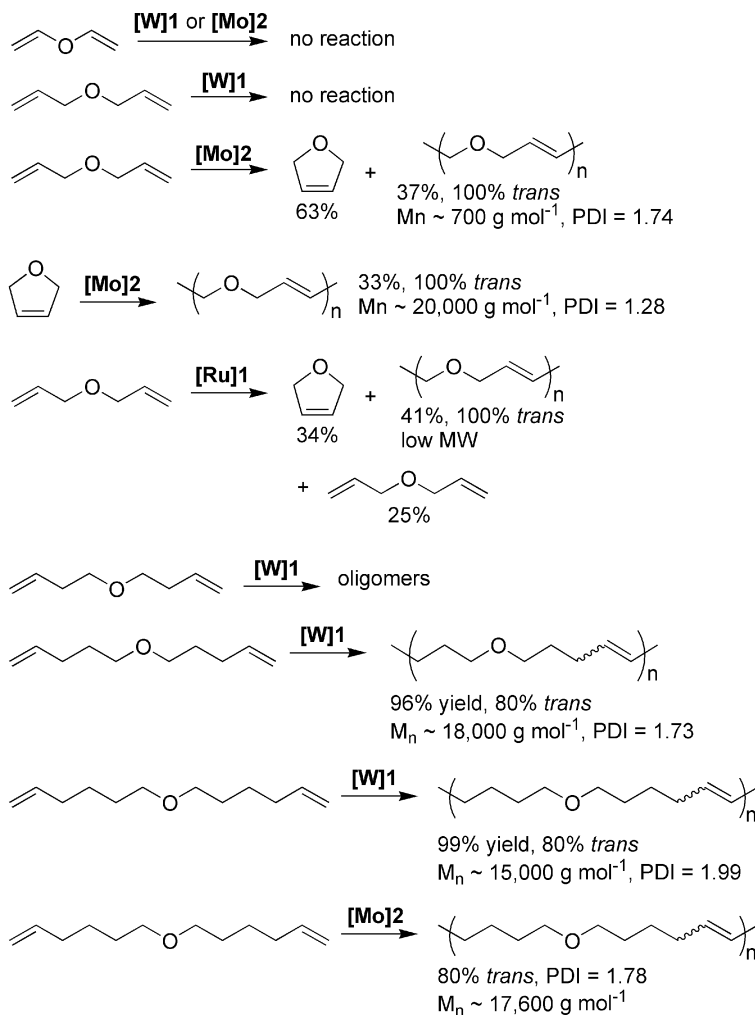
Irreversible coordination or reaction of a functional group with the catalyst will deactivate the catalyst towards olefin metathesis, which will, of course, prevent ADMET from occurring. As an example, the reaction of methyl acrylate with **[W]1** produces a stable tungstacyclobutane in which the carbonyl oxygen is coordinated to the tungsten atom [152]. Additionally, catalyst **[W]1** will react in a Wittig fashion with carbonyl compounds, including esters, to make the metathesis-inactive tungsten-oxo complex and the corresponding olefin [49]. This section will report the applicability of various metathesis catalysts to ADMET polymerization of functionalized dienes.

3.9.7.1

Ethers, Acetals, and Alcohols

Ethers were the first functionalized dienes to be successfully polymerized via ADMET with Schrock's catalysts and are indeed polymerizable with the highly electrophilic tungsten catalyst **[W]1** [153]. However, at least three methylene spacers are required between the oxygen atom and the olefins for successful polymerization with Schrock's catalysts. These polymers were capable of cross-linking by photochemical or chemical means [154]. The use of **[Mo]2** yielded similar results, although the polymerization occurs at a rate estimated at 10 times faster than that with **[W]1** [155]. Catalyst **[Mo]2** also promotes the polymerization of diallyl ether to a low-molecular-weight polymer. Complex **[Ru]1** also promotes RCM and ADMET of diallyl ether, but in this case 25% of unreacted monomer was also recovered [97]. The major reaction pathway for both **[Mo]2** and **[Ru]1** was RCM to yield 2,5-dihydrofuran. ROMP of 2,5-dihydrofuran produces a much higher molecular weight polymer in 33% yield with a lower polydispersity compared to the same polymer produced via ADMET. These results support the stepwise condensation mechanism of ADMET polymerization. In contrast, no metathesis reactions occur between diallyl ether and **[W]1**. Neither **[W]1** nor **[Mo]2** promotes metathesis of divinyl ether. The results are summarized in Scheme 3.9-35. The high-molecular-weight polyethers from di-4-pentenyl and di-5-hexenyl ether were amenable to chemical and photochemical cross-linking. Copolymers of these monomers with 1,9-decadiene were also successfully prepared by ADMET polymerization.

ADMET with **[Mo]2** has also been conducted on dienes containing multiple ether functionalities [155] and on macromonomer dienes synthesized by anionic living polymerization of THF [156]. Acetals are also amenable to ADMET chemistry, and an acetal-containing diene has been polymerized with **[Ru]1** to give the ADMET polymer ($M_n = 23,000 \text{ g mol}^{-1}$) in quantitative yield (Scheme 3.9-36) [97]. A number of alcohols have been polymerized with **[Ru]1** [157]. The hydroxyl group can be primary, secondary, or tertiary.

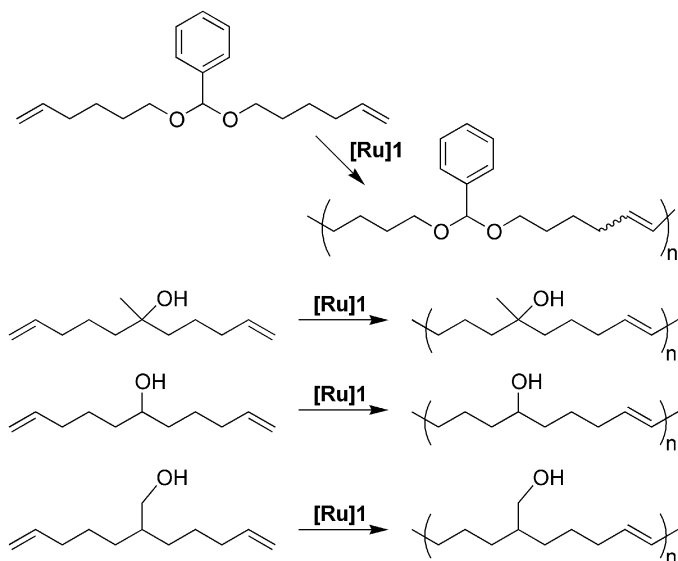


Scheme 3.9-35. ADMET polymerization of ethers.

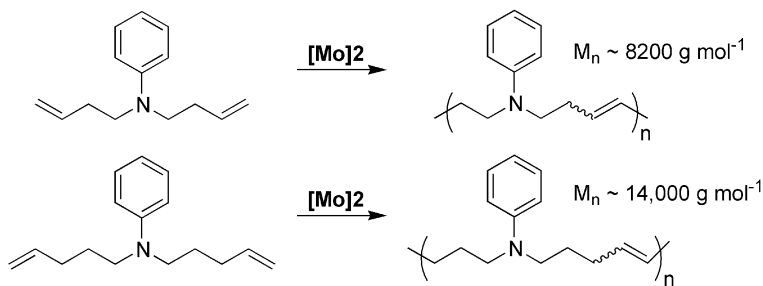
3.9.7.2

Amines

The synthesis of ADMET polyamines has been relatively unexplored, with the exception of several aromatic tertiary amines. The high Lewis basicity of amines would seem to render them apt to coordinate to electrophilic metal atoms, perhaps restricting the high conversions necessary for ADMET polymerization. It is known that diallylamine does not undergo reaction with **[Mo]2**, whereas *N*-phenyl-diallylamine cyclizes in high yield. Correspondingly, *N*-phenyl-di-3-butenylamine and *N*-phenyl-di-3-pentenylamine smoothly underwent ADMET polymerization to



Scheme 3.9-36. ADMET polymerization of acetal and alcohol dienes.



Scheme 3.9-37. ADMET polymerization of aromatic tertiary amines.

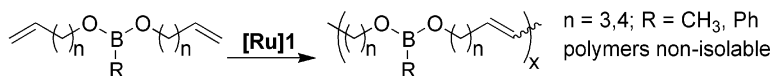
relatively high-molecular-weight polymers with approximately 80% *trans* stereochemistry about the backbone double bonds (Scheme 3.9-37). ADMET of amines with the ruthenium olefin metathesis catalysts has yet to be explored in detail, but it appears that protection of the amine is necessary to achieve polymer [158].

Dienes containing cyclic phosphazenes have been polymerized by ADMET with [Ru]1 and [Ru]2, and little difference in terms of molecular weight was found between the polymers produced by the two complexes [159].

3.9.7.3

Boronates

Four boronate monomers have been polymerized using [Ru]1 (Scheme 3.9-38) [160]. The materials were difficult to work up and characterize, however, presum-



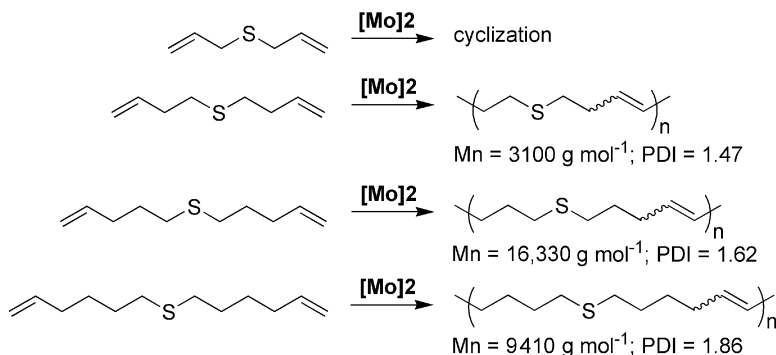
Scheme 3.9-38. ADMET polymerization of boronates.

ably due to backbiting reactions between the boronate groups to liberate cyclic oligomers.

3.9.7.4

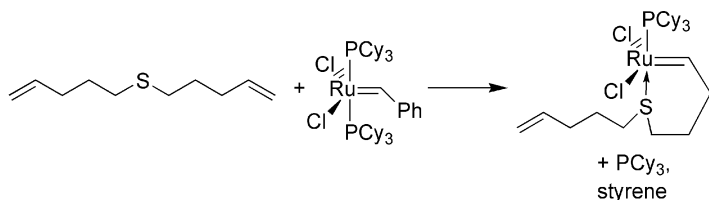
Thioethers

A series of thioethers has been polymerized with molybdenum catalyst **[Mo]2** (Scheme 3.9-39) [161]. A kinetic study with these monomers has also been performed and will be discussed in Section 3.9.10. Di-5-hexenylsulfide was copolymerized with 1,9-decadiene to produce a random copolymer with M_n of 34,940 g mol^{-1} and PDI of 1.31 [161].



Scheme 3.9-39. ADMET polymerization of thioethers.

The thioether monomers do not undergo metathesis with **[Ru]1**, however [162]. A stable S–Ru chelate complex is suggested as the reason for the inactivity. A Ru–S bond would be expected to be stronger than a Mo–S bond according to the size and polarizability of the two metals. Monitoring the reactions with ^{31}P NMR spectroscopy indicated that a new alkylidene and free phosphine are formed during the reaction, which is consistent with the proposed chelation event and the fact that one phosphine of **[Ru]1** is labile (Scheme 3.9-40) [118].



Scheme 3.9-40. Suggested stable chelate formed by reaction of **[Ru]1** with di-5-pentenylsulfide.

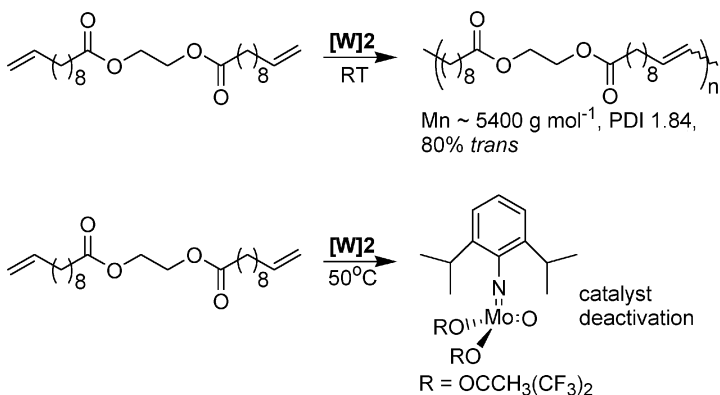
3.9.7.5

Carbonyl Compounds

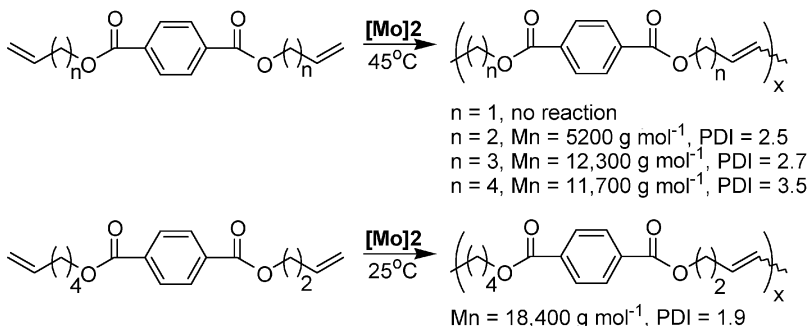
Polymers containing the carbonyl moiety are discussed below, with the exception of amide- and peptide-derived polymers, which are discussed in Section 3.9.12.

Esters Many unsaturated polyesters have been produced via ADMET polymerization. Complexes [W]1 and [W]2 are known to undergo Wittig-like reactions with esters under proper conditions, and this reaction has been used for cyclization of unsaturated esters using stoichiometric quantities of the tungsten complex [2]. Nevertheless, polymerization of ethylene glycol di-10-undecenoate with [W]2 at room temperature proceeded to give the expected ADMET polymer, whereas at 50 °C the Wittig-like reaction occurred and resulted in catalyst deactivation (Scheme 3.9-41) [163].

A series of aromatic ester dienes has been polymerized with [Mo]2 (Scheme 3.9-42) [96]. Schrock's molybdenum catalysts do not undergo the Wittig-like reac-



Scheme 3.9-41. ADMET of an unsaturated diester with [W]2.

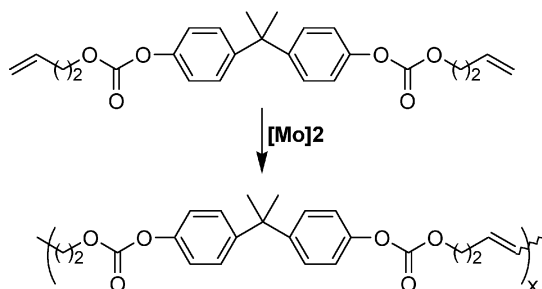
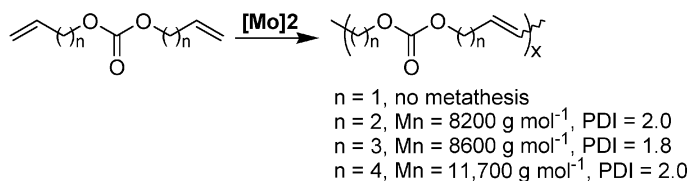


Scheme 3.9-42. ADMET polymerization of aromatic ester dienes with [Mo]2.

tion with esters but do so with ketones and aldehydes under certain conditions. In some cases, the PDI of the polymers was abnormally high.

Catalysts **[Ru]1** and **[Ru]2** also polymerize ester dienes with the ester both in the main chain [164] and as a pendant group [165] (see Section 3.9.11). A series of liquid crystalline polyesters has been synthesized via ADMET with **[Ru]1** [166]. ADMET is actually quite well suited to synthesis of liquid crystals. The alkenyl chains used for ADMET monomers can be easily attached to a rigid mesogen, which upon polymerization gives the alternating flexible-rigid-flexible structural motif often employed for liquid crystalline polymers.

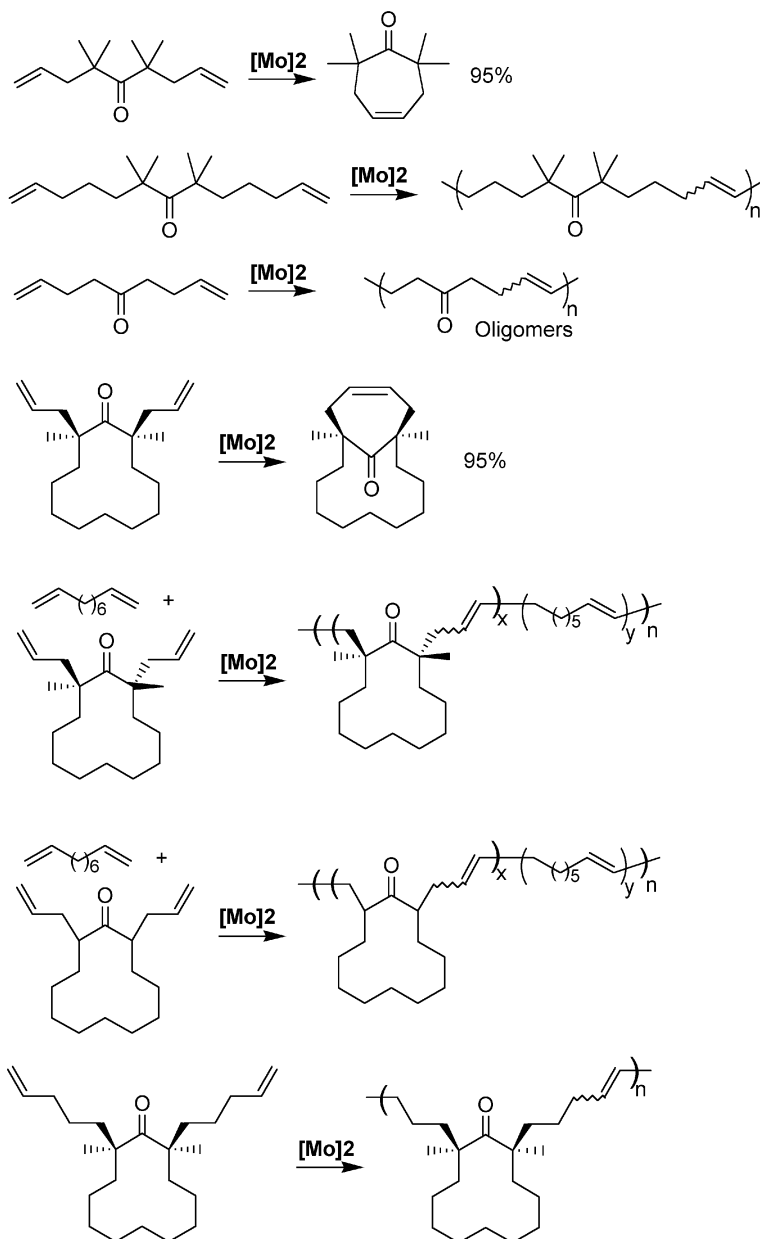
Carbonates A series of polycarbonates has been synthesized by ADMET polymerization with **[Mo]2** (Scheme 3.9-43) [167]. In this case, only two methylene spacers between the carbonate group and the olefin are required for ADMET polymerization to occur. A diene containing a bisphenol-A unit was polymerized to a polymer with M_n 15,800 g mol^{-1} and PDI of 1.9.



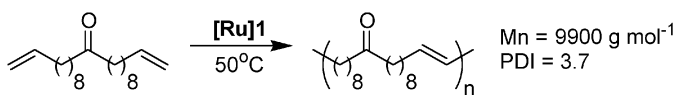
Scheme 3.9-43. ADMET polymerization of carbonate dienes.

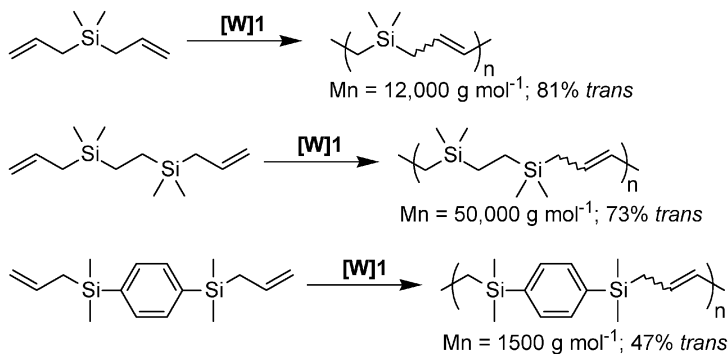
Ketones Ketones are known to react in a Wittig-like fashion with **[Mo]2** in some cases. Nevertheless, ADMET polymerization does proceed for some ketone dienes [168], and, not surprisingly, results are best with hindered ketones. Some of these monomers were also copolymerized with 1,9-decadiene [169]. The results are summarized in Scheme 3.9-44.

Unhindered ketone-containing dienes have been successfully polymerized with **[Ru]1** and **[Ru]2** (Scheme 3.9-45) [164].



Scheme 3.9-44. ADMET polymerization of ketone dienes.

Scheme 3.9-45. Polymerization of an unhindered ketone with **[Ru]1**.



Scheme 3.9-47. ADMET polymerization of silanes.

however. As expected, the copolymer contains no adjacent vinylsilane repeat units due to the inaccessibility of the required metallacyclobutane.

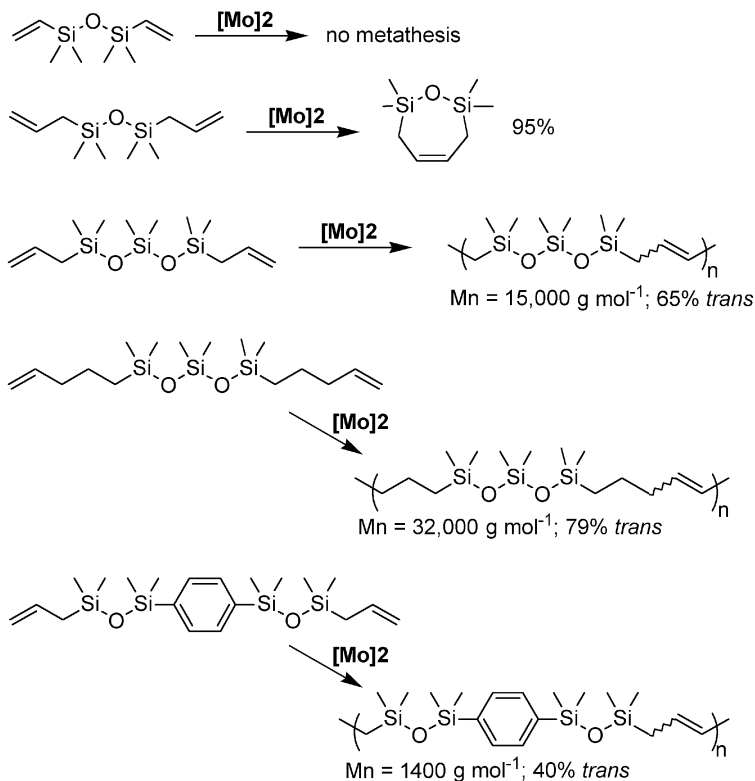
Incorporation of methylene spacers between the silicon atom and the olefin effectively reduces the steric congestion about the required tungstacyclobutane, and thus these monomers were successfully polymerized via ADMET (Scheme 3.9-47) [78]. As is usually observed for ADMET polymerization, the stereochemistry of the polymer double bonds is predominantly *trans*, except in the case of 1,4-bis-(dimethylallylsilyl)benzene, which produced a polymer with 47% *cis* configuration about the backbone olefins.

Siloxanes Siloxanes are also amenable to ADMET polymerization with catalyst [Mo]2 and show trends similar to those of the silanes [171]. 1,1,3,3-Tetramethyl-1,3-divinyl-disiloxane undergoes no productive metathesis, and 1,3-diallyl-1,1,3,3-tetramethyldisiloxane cyclizes in high yield. However, longer di- and trisiloxane monomers will polymerize via ADMET, as shown in Scheme 3.9-48. Some of these polymers degrade over time via intrachain siloxane exchange reactions to form cyclic oligomers. Ring-chain equilibria are well known for polysiloxanes [172].

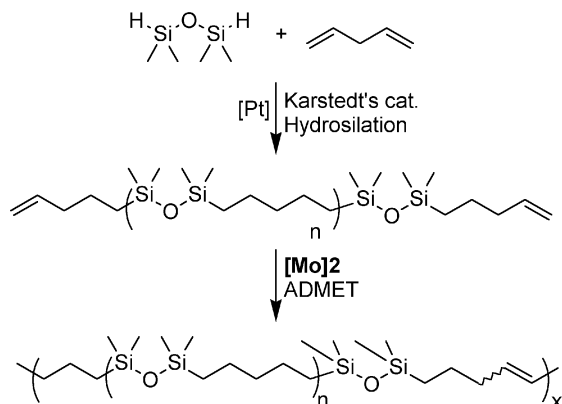
ADMET has been used to condense a telechelic oligomer formed by hydrosilation of 1,4-pentadiene with 1,1,3,3-tetramethyldisiloxane, as shown in Scheme 3.9-49 [171].

ADMET has also been used to synthesize copolymers containing backbone siloxanes and methoxy-substituted silanes (Scheme 3.9-50) [173]. The methoxy-substituted silanes slowly cross-link upon atmospheric exposure to form siloxane cross-links, a well-known phenomenon in the silicone sealant industry [174].

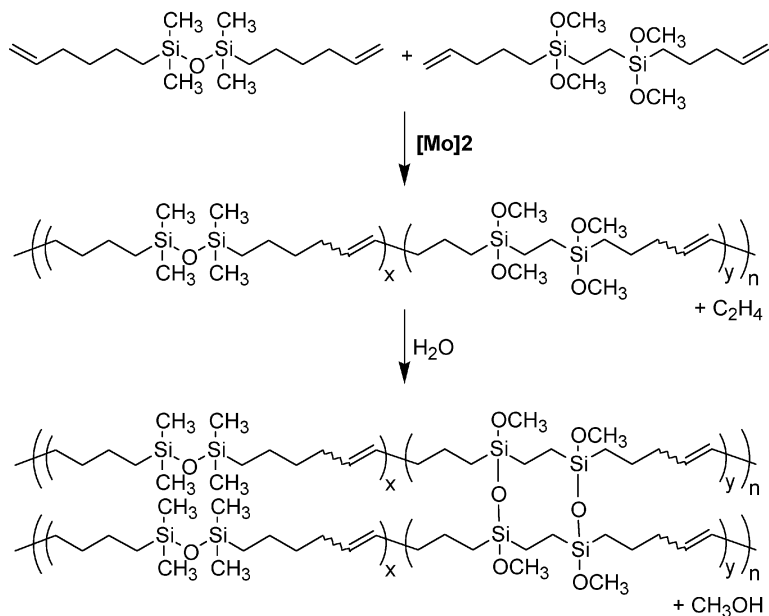
Silyl chlorides Although highly polar and reactive, the silicon-chlorine bond is inert to metathesis conditions with [Mo]2. This allows for preparation of reactive and cross-linkable polymers for potential applications in sealants and adhesives, for example.



Scheme 3.9-48. ADMET polymerization of siloxane-containing dienes.

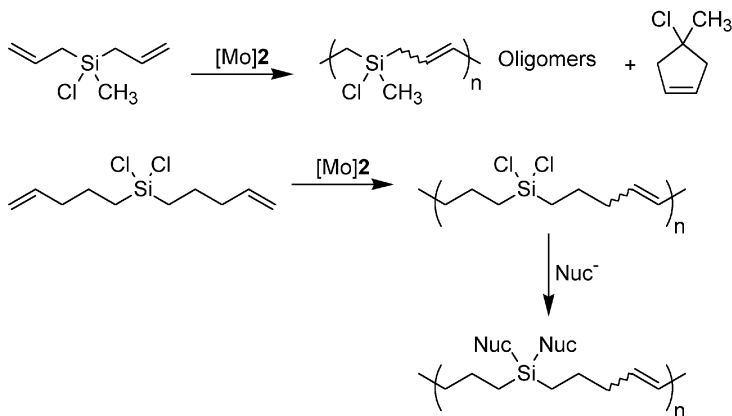


Scheme 3.9-49. ADMET polymerization of a telechelic carbosiloxane diene.

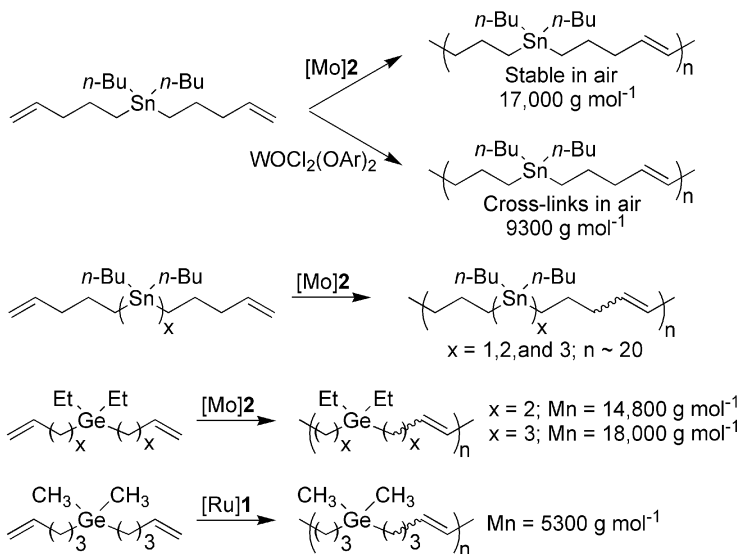


Scheme 3.9-50. Silicon-containing polymers with latent reactive sites.

Dienes containing silicon atoms with one or two chlorine atoms are polymerizable via ADMET with complex [Mo]2 (Scheme 3.9-51) [175]. Monomers with at least two methylene spacers between the olefin and silicon atom readily polymerize to high-molecular-weight polymers [176]. These polymers can then be quantitatively functionalized with various nucleophilic reagents, such as alkyl and phenyl lithium reagents and alkoxy and phenoxy ions.



Scheme 3.9-51. ADMET polymerization of dienes containing Si–Cl bonds and subsequent nucleophilic substitution.



Scheme 3.9-52. ADMET polymerization of tin- and germanium-containing dienes.

3.9.7.8

Organometallic Compounds

Several organometallic dienes have successfully been prepared by ADMET polymerization. Carbostannane monomers have been polymerized with **[Mo]2** (Scheme 3.9-52) [177]; in fact, these monomers can act as co-catalysts in ADMET with classical metathesis catalysts. In this case, the monomer both activates the catalyst and condenses to form high polymer. The presence of Sn–Cl bonds formed during the activation of the classical catalyst was inferred by observed gelation of these polymers by hydrolysis of tin-chlorine bonds to form tin-oxygen-tin cross-links. The analogous polymer made with **[Mo]2** does not cross-link. A polymer with Sn–Sn bonds was also produced with complex **[Mo]2** [178]. Similar germanium-containing polymers have been prepared by ADMET polymerization with **[Mo]2** and **[Ru]1**, with **[Mo]2** giving the best results [179].

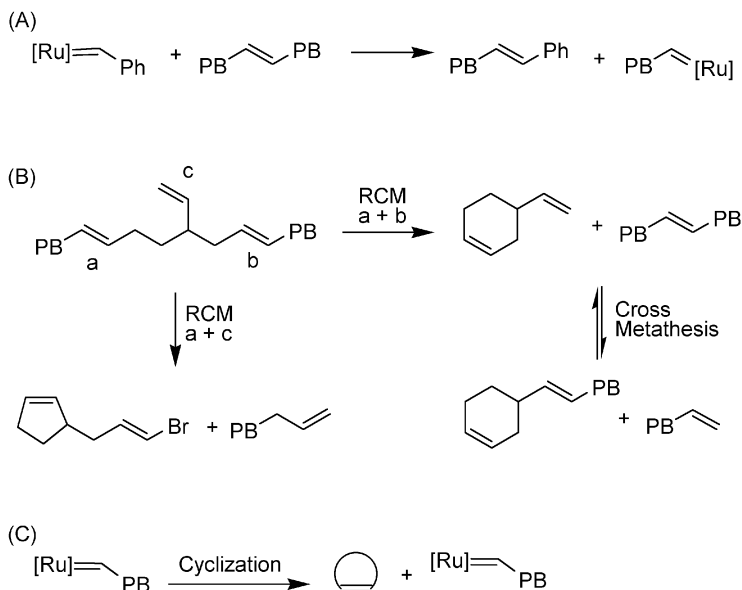
3.9.8

Retro-ADMET: Towards Recycling of Unsaturated Polymers with Well-Defined Metathesis Catalysts

Metathesis degradation of unsaturated polymers is an attractive approach to recycling unsaturated polymers into other useful materials, and it had been investigated by a number of workers prior to the development of the Lewis-acid-free Schrock metathesis catalyst **[W]1** [180]. The very clean and selective nature of metathesis with Schrock's catalysts warranted a reinvestigation of the subject with these complexes.

Early in the history of ADMET with Schrock's catalysts, it was shown that these catalysts are capable of depolymerizing ADMET polyoctenamer and commercial samples of polybutadiene, poly-*trans*-isoprene, polynorbornene, and Kraton™, a polybutadiene/polystyrene diblock copolymer [76]. These depolymerizations were conducted by bubbling ethylene gas through the reaction flask or by applying a certain pressure of ethylene to a toluene solution of the polymer and [W]1, depending on the polymer in question. The products consist of monomer and some oligomers. For Kraton™, the product consists of the polystyrene block and polybutadiene oligomers. Depolymerization of polynorbornene yields a polymer of lower molecular weight than the starting material, due to less-effective metathesis at the sterically shielded backbone double bonds of this polymer. While this is interesting work, the sensitivity of the complex would seem to limit the possibilities for this chemistry in recycling.

The less-sensitive catalyst [Ru]1 also effectively depolymerizes 1,4-polybutadiene with ethylene [181]. 1,5-Hexadiene was produced in greater quantities with [Ru]1 than in the previous study using [W]1, and the extent of the depolymerization increased under higher pressures of ethylene. Above 400 psi of ethylene, however, the extent of conversion decreases, possibility due to bimolecular decomposition known to occur for the methylene-carbene complex of [Ru]1. Furthermore, it was found that commercial polybutadiene can be depolymerized in the absence of ethylene and solvent with [Ru]1 (Scheme 3.9-53) [182]. In this case, cyclics and



Scheme 3.9-53. Depolymerization of polybutadiene with [Ru]1 in the absence of ethylene and solvent; PB: polybutadiene. (A) Incorporation of initial benzylidene of [Ru]1 as an end group. (B) RCM pathways to cyclic end groups. (C) Production of cyclics.

linear oligomers are formed. The chain ends of the linear oligomers are provided by the benzylidene residue of **[Ru]1** and by the ~1% of 1,2-linkages in the commercial polybutadiene. The 1,2-linkages undergo RCM reactions to form low-strain cyclic end groups.

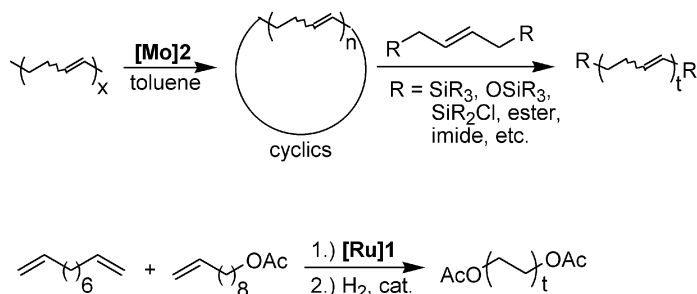
Coughlin et al. have recently found that **[Ru]2** is a more effective depolymerization catalyst than **[Mo]2** or **[Ru]1** for the depolymerization of either polyisoprene or polybutadiene blocks of triblock copolymers of the type polystyrene-polyene-polystyrene [183]. Unlike **[Mo]2** and **[Ru]1**, **[Ru]2** is capable of depolymerizing sulfur-cross-linked *cis*-1,4-polyisoprene to oligomers containing approximately 10 repeat units. This field represents a potentially useful recycling technique, especially if the cost and robustness of the catalysts can be improved.

3.9.9

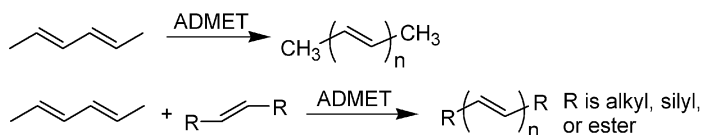
Telechelic Oligomers via ADMET

ADMET is an effective means of synthesizing telechelic oligomers, which are oligomers possessing functionalized end groups. These materials are sought after as macromonomers in the synthesis of segmented polymers. For example, condensation polymerization of a “soft” (low T_g) telechelic diol with a “hard” (high T_g) telechelic diisocyanate would give an $(AB)_n$ block copolymer connected by urethane linkages that could have potential use as a thermoplastic elastomer [184, 185]. Telechelics are notoriously difficult to produce with functionality close to 2.0, which means that each chain has exactly two reactive functional groups. Functionality of 2.0 is required for the stoichiometric balance needed in polycondensation reactions for which telechelics are used as monomers [186].

Unsaturated telechelic oligomers of polybutadiene can be prepared by ADMET of 1,5-hexadiene with an appropriate mono- or difunctional olefin with **[W]2** and **[Mo]2** [187, 188]. An alternate approach is to polymerize 1,5-hexadiene to ADMET polybutadiene then to react this polymer with an appropriate functionalized olefin. The mechanism is believed to proceed by cyclization of polybutadiene, followed by cross-metathesis of the cyclic polymer with the functionalized olefins, as proposed by Calderon (Scheme 3.9-54) [189]. In some cases, formation of the telechelics is



Scheme 3.9-54. Synthesis of telechelic oligomers via ADMET.



Scheme 3.9-55. Polymerization of 2,4-hexadiene with a 1,2-disubstituted olefin to give polyacetylene telechelics.

incomplete and some amount of cyclic polybutadiene remains in the polymer. This technique is most applicable to the synthesis of short telechelic oligomers, with up to five repeat units per chain. The end functionality can be silane, siloxy, ester, imide, silyl chloride, and other functional groups.

Telechelic oligomers can also be prepared with **[Ru]1**. Polyethylene oligomers end capped with ester groups were prepared by ADMET of 1,9-decadiene in the presence of 9-decenyl acetate, followed by selective hydrogenation of the olefins [164]. Low T_g telechelic oligomers of ethylene and isobutylene have also been prepared by this method [190].

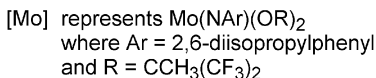
Polymerization of 2,4-hexadiene in the presence of 1,2-disubstituted olefins leads to telechelic polyacetylenes (Scheme 3.9-55) [191]. Thus, polyacetylene oligomers terminated with alkyl groups, silanes, and esters were produced via ADMET chemistry. However, terminal olefins are not capable of terminating these polyacetylene oligomers due to the deactivation of **[Mo]2** in the presence of terminal conjugated alkenes.

3.9.10

Kinetics and Mechanism

More detailed knowledge of mechanism and kinetics of ADMET polymerization with the various metathesis catalysts allows a more rational approach to monomer design and catalyst choice. The mechanism of ADMET polymerization is simply adapted from the accepted mechanism for olefin metathesis and is illustrated for **[Mo]2** in Scheme 3.9-56.

Kinetic analysis of ADMET gives insight into details of the catalysis not represented by the proposed mechanism. However, several aspects of the conditions employed for ADMET polymerization render careful tracking and kinetic analysis of the reaction difficult. First, ADMET is usually conducted in the absence of solvent in order to minimize cyclization and promote intermolecular condensation. This limits the usefulness of NMR spectroscopy to study ADMET polymerization, since NMR works best with lower concentrations and some amount of deuterated solvent. NMR analysis has proven useful in the study of model reactions with Schrock's catalysts, however [192]. Collection of samples at various times is also cumbersome and inconvenient due to the sensitivity of some of the metathesis catalysts to air and moisture. Finally, the kinetic analysis is complicated due to the decrease in reaction rate that accompanies the increase in viscosity that occurs upon polymerization of the monomer in bulk.



Scheme 3.9-56. Mechanism of productive ADMET with [Mo]2.

The most convenient way to measure the kinetics of ADMET is to measure the rate of evolution of ethylene from a polymerization of an α,ω -diene at ambient pressure. The degree of polymerization can be directly calculated from the volume of ethylene released, and the degree of polymerization versus time is the primary kinetic measurement for ADMET polymerization. Since it is a volume that is measured, these kinetic experiments cannot be conducted under vacuum. Thus, these measurements are not a representation of the kinetics of ADMET under vacuum but are very useful for comparing the activities of various catalysts.

This approach was first used to quantify the difference in activity of **[Mo]2** and **[Ru]1** for ADMET of 1,9-decadiene [162]. The kinetics of catalyzed polycondensations is well known, and it is a general feature that the degree of polymerization proceeds linearly with time [193]. For this study of ADMET, the plots of the degree of polymerization versus time were linear until the degree of polymerization increased to approximately five, at which point the viscosity of the system signifi-

Tab. 3.9-4. Measured rates of ADMET polymerization (k_p)^a of various monomers.

Monomer	k_p [Mo]2 (l mol ⁻¹ s ⁻¹)	k_p [Ru]1 (l mol ⁻¹ s ⁻¹)
1,9-Decadiene	2.4×10^{-3}	1.0×10^{-4}
Di-4-pentenyl ether	1.2×10^{-3}	6×10^{-6}
Di-5-hexenyl ether	1.5×10^{-3}	1×10^{-5}
Di-4-pentenyl sulfide	2×10^{-4}	0
Di-5-hexenyl sulfide	1.3×10^{-3}	0
1,5-Hexadiene	4.1×10^{-3}	Cyclodimerization

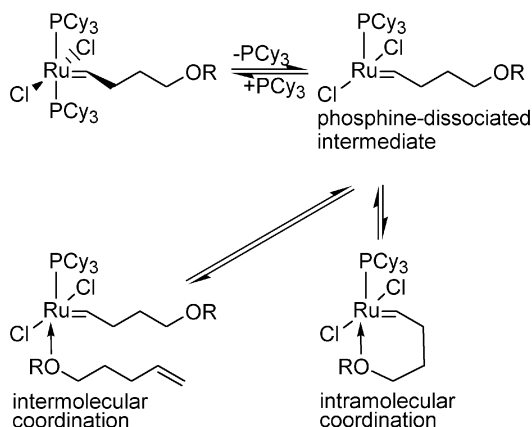
^a k_p measured at 26 °C in bulk monomer. Monomer:catalyst 450:1.

cantly increases. The linearity of the plots of degree of polymerization versus time indicates that ADMET is a quasi-second-order reaction at low conversions, in line with traditional externally catalyzed polycondensations. [Mo]2 promotes ADMET of 1,9-decadiene at a rate approximately 24 times that of [Ru]1 under these conditions (Table 3.9-4). Furthermore, [Mo]2 polymerizes 1,5-hexadiene 1.7 times faster than 1,9-decadiene, and [Ru]1 only cyclodimerizes 1,5-hexadiene to 1,5-cyclooctadiene.

Monomers with coordinating functionality undergo polymerization more slowly than hydrocarbon monomers. For [Mo]2, di-4-pentenyl ether, di-5-hexenyl ether, and di-5-hexenyl sulfide all polymerize at a similar rate that is only slightly lower than that of 1,9-decadiene. Di-4-pentenyl sulfide, however, polymerizes an order of magnitude slower than 1,9-decadiene. Surprisingly, it was found that coordinating functionality influences the rate of polymerization to a much greater extent with [Ru]1 than with [Mo]2. Di-5-hexenyl ether polymerizes an order of magnitude slower than 1,9-decadiene, and di-4-pentenyl ether polymerizes at only 6% the rate of 1,9-decadiene. Both of the dialkenyl sulfide monomers completely shut down the polymerization with [Ru]1. Thus, although [Ru]1 is tolerant of a greater variety of functional groups than [Mo]2, the retarding effect of coordinating functionality is actually greater for [Mo]2, at least for ethers and sulfides.

Since the polymerizations were conducted in bulk monomer, the effect of dielectric constant of the monomers could also be a factor in the rate of polymerization. However, the dielectric constant of the ethers and sulfides is higher than that of the hydrocarbon monomers, and the ruthenium catalysts are known to be more active in media with high dielectric constants [118, 194]. Based on this data, it seems unlikely that dielectric constant of the monomer is responsible for the large reduction in polymerization rate.

Reversible coordination of the heteroatom to a vacant coordination site of [Ru]1 is the most likely cause of the slower kinetics of ADMET of functional monomers with this complex. Phosphine dissociation from the metal center is required before an olefin can coordinate to the metal for metathesis with the ruthenium complexes. Accordingly, several chelate complexes have been isolated and characterized in which an olefin or a heteroatom of the carbene fragment has replaced an axial phosphine of complexes [Ru]1 and [Ru]2 [111, 151]. Thus, heteroatoms can compete with olefins for the open coordination site of the phosphine-dissociated



Scheme 3.9-57. Reversible coordination of heteroatoms to the metal atom in complex **[Ru]1**.

complex and thus retard the rate of metathesis (Scheme 3.9-57; see also Scheme 3.9-13). Reversible coordination of heteroatoms to the ruthenium complexes probably occurs both intramolecularly and intermolecularly in ADMET due to the high concentration of monomer in bulk conditions. A similar effect was observed for ROMP of cyclooctenes with coordinating functionality at the 5-position [195]. On the other hand, **[Mo]2** is less apt to form a five-coordinate complex due to the steric influence of the bulky ligands. An approaching olefin is believed to only fleetingly coordinate to the metal of **[Mo]2** before forming the molybdacyclobutane. Thus, the effect of reversible coordination to the metal center of **[Mo]2** is not as significant as with **[Ru]1**, even though the molybdenum atom is more electrophilic than the ruthenium atom.

The ADMET activity of the second-generation ruthenium catalyst, **[Ru]2**, falls between that of **[Ru]1** and **[Mo]2** [196]. A comparison of **[Ru]1** and **[Ru]2** revealed that **[Ru]2** promotes ADMET faster than **[Ru]1** at temperatures of 45 °C and higher; **[Ru]1** is the faster of the two at 30 °C. At 75 °C, **[Ru]2** promotes ADMET 6.5 times faster than **[Ru]1** (Figure 3.9-3).

The nonlinearity of the Arrhenius plot of the rate of ADMET versus temperature (Figure 3.9-3) suggested that more than one elementary process was occurring. Furthermore, a conspicuous induction period exists at low conversions for **[Ru]2** at 30–75 °C that is absent with **[Ru]1** (Figure 3.9-4). The elapsed time before the maximum rate of ADMET was achieved decreased with increased temperature. This induction period is due to the slow kinetics of phosphine dissociation of **[Ru]2** compared to **[Ru]1**. These results were unexpected at the time; in fact, it had been proposed that the higher activity observed with **[Ru]2** was due to faster phosphine dissociation.

Contemporary results published by the Grubbs group are in agreement with the ADMET kinetic data. This detailed study showed that although the phosphine-dissociated complex forms more slowly for **[Ru]2** than for **[Ru]1**, the dissociated

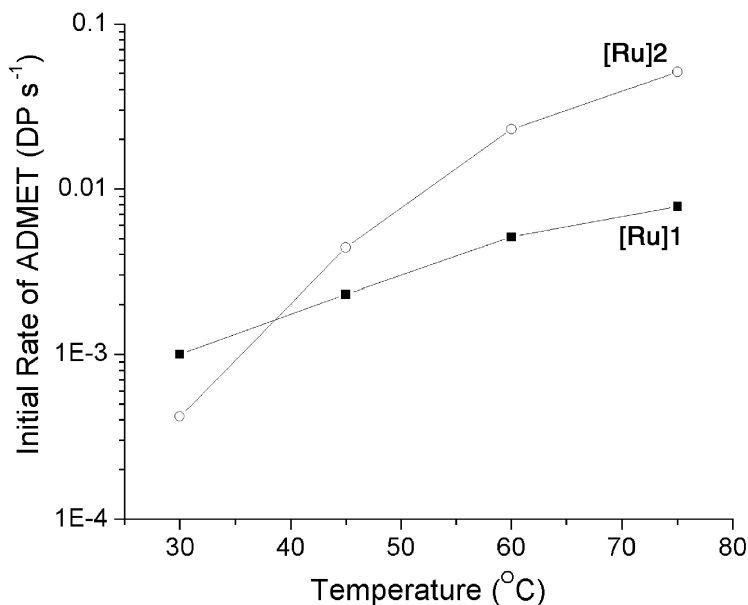


Fig. 3.9-3. Temperature dependence of the rate of ADMET of 1,9-decadiene with ruthenium complexes. Reprinted with permission from ACS [196]

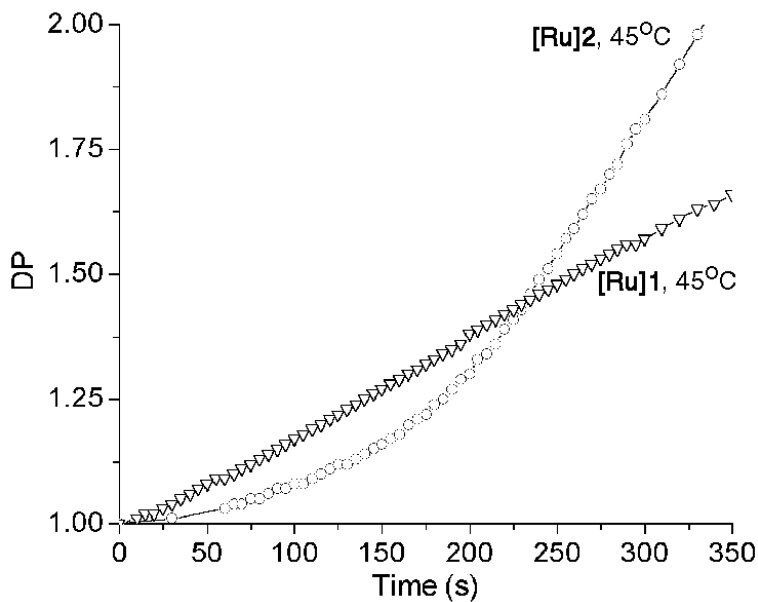
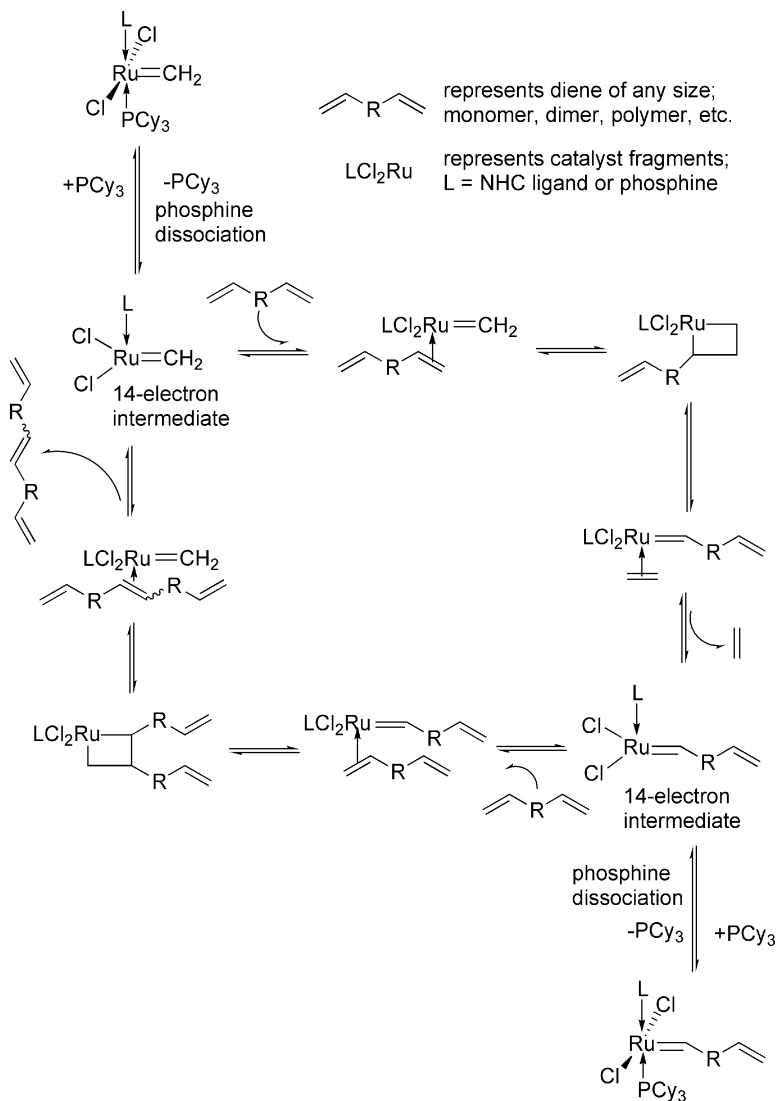


Fig. 3.9-4. Degree of polymerization vs. time plot at low conversion for ADMET polymerization of 1,9-decadiene with ruthenium complexes showing induction period for [Ru]2. Reprinted with permission from ACS [196]

complex with an NHC ligand is more likely to bind an olefin and thus undergo metathesis than to be recaptured by a phosphine ligand. The opposite is true for **[Ru]1**, which is more likely to be recaptured by a phosphine than to bind an olefin and undergo metathesis. These findings led to a revision of the ADMET mechanism with ruthenium catalysts that included the critical aspect of phosphine dissociation (Scheme 3.9-58).



Scheme 3.9-58. Revised mechanism of ADMET with ruthenium olefin metathesis catalysts. L = PCy_3 , **[Ru]1**; L = SIMes, **[Ru]2**. Initial exchange of benzylidene carbene complex not shown.

Developments in catalyst design will provide even more ADMET-active metathesis catalysts. For example, [Ru]3, with a slightly modified NHC ligand, appears to promote ADMET faster than [Ru]2 [197]. It is important to note that the final molecular weight of a polymer is far more important than the initial rate of metathesis with a particular catalyst. Thus far, however, the catalysts that promote ADMET at higher initial rates also produce ADMET polymers of higher final molecular weights.

3.9.11

Modeling Polyolefins with ADMET

The wide range of materials available through the polymerization of various commodity olefins, such as ethylene, is a testament to the usefulness of organometallic polymerization methods. ADMET has been utilized as a catalytic polymerization method to synthetically model commercially important polyolefins, since linear polyethylene segments are produced upon hydrogenation of unsaturated ADMET polymers in which linear alkenyl groups flank a functional or pendant group. The polymers are equivalent to sequence-specific copolymers of ethylene and another monomer. However, modeling of non-sequence-specific copolymers can be prepared via ADMET copolymerization of a functional diene and a non-functional linear diene, such as 1,9-decadiene. Utilizing this unique condensation polymerization provides a route to completely linear polymers that in many cases are not producible by chain or coordination polymerization methods. The desire to understand the molecular origins of mechanical and other material properties for polyolefins makes synthetic modeling in precise ways valuable to scientists in industry and academia.

3.9.11.1

Hydrogenation of ADMET Polymers

In order to provide realistic models of polyolefins produced by chain polymerization, quantitative hydrogenation of the unsaturated ADMET backbone is essential. Fortunately, several methods have been developed that provide quantitative hydrogenation within the limits of detection of the methods used to analyze the saturated polymers, namely, ^1H and ^{13}C NMR and IR spectroscopies.

Diimide reduction is a viable method for quantitative hydrogenation of unsaturated linear ADMET polymers that was utilized to hydrogenate ADMET polyoctenamer to linear polyethylene [198, 199]. Two treatments of the unsaturated polymer with *p*-toluenesulfonylhydrazide and tripropylamine (2 equivalents) provided the saturated polymer with no detectable olefins. The melting point of the linear polyethylene thus produced is a good indicator of the extent of hydrogenation. Linear polyethylene displays peak melting transitions between 130 °C and 140 °C. The melting points obtained for ADMET polyethylene obtained by diimide reduction ranged from 130.7 °C ($M_n = 2400 \text{ g mol}^{-1}$) to 133.9 °C ($M_n =$

15,000 g mol⁻¹), in line with linear polyethylene. This hydrogenation technique is useful for polymers that become insoluble after reduction, as the polymer can be precipitated directly into methanol and then re-crystallized from an appropriate high-boiling solvent, such as toluene or xylene. This hydrogenation technique is general and has also been used to hydrogenate a number of ROMP polymers.

Catalytic hydrogenation using hydrogen gas and an appropriate metal-based catalyst has also been useful for hydrogenating ADMET polymers [200]. The Pd/C reagent is capable of quantitatively hydrogenating ADMET polymers at H₂ pressures of 250–600 psi. Repeated treatments may be necessary. This technique is useful for polymers that remain soluble after reduction, in that the solution of polymer may be separated from the catalyst by simple filtration.

Another useful heterogeneous hydrogenation catalyst may be prepared directly from ADMET polymerization mixtures with [Ru]1 or [Ru]2 by simply adding chromatographic silica to the polymerization mixture, diluting in an appropriate solvent, and applying hydrogen at pressures of 200–500 psi [164]. Ruthenium-based hydrogenation catalysts are well known in the literature [201–204], but neither the exact nature of this heterogeneous catalyst nor the mechanism of the hydrogenation is known. This simple modification of the metathesis catalyst is convenient in that no additional catalyst is required, no workup of the initial unsaturated ADMET polymer is required, and removal of the metathesis catalyst is achieved by simple filtration of the heterogeneous catalyst from the hydrogenation reaction mixture. This technique is best used for polymers that remain soluble after reduction, because the removal of the heterogeneous catalyst in boiling solvents required for linear polyethylene, for example, is procedurally difficult.

Several studies have shown that the ruthenium catalysts [Ru]1 and [Ru]2 can be converted to hydrogenation catalysts without heterogenization onto a solid support [201, 205, 206]. This strategy has not yet been explored in the context of hydrogenating ADMET polymers, but it seems promising for insoluble saturated polymers. Homogeneous catalysis of this sort retains the benefits of the [Ru]1-SiO₂ system with the added benefit that the homogeneous catalyst can be separated from the saturated polymer by precipitation without the need to filter off a solid reagent.

The best homogeneous hydrogenation catalyst used so far for insoluble polyolefins is Wilkinson's catalyst, RhCl(PPh₃)₃ [207], at hydrogen pressures of 200–1200 psi and temperatures up to 160 °C [208]. Wilkinson's catalyst is commercially available or easily synthesized from commercially available reagents and is air stable as a solid. This catalyst is easily separated from insoluble polyolefins by precipitation from an appropriate high-boiling solvent into acidic methanol at 40 °C.

3.9.11.2

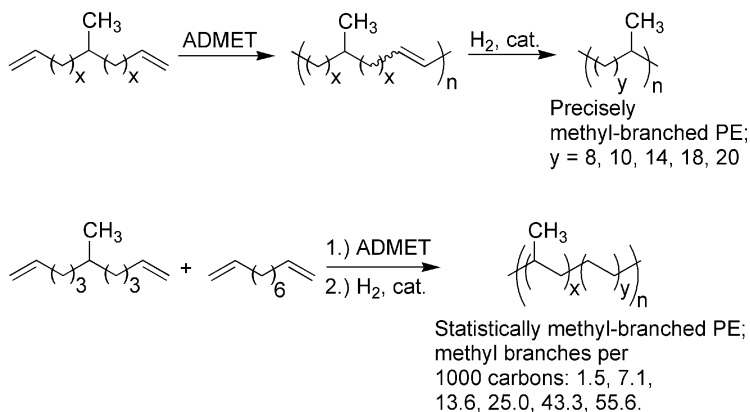
Branched Polyethylene

Polyethylene (PE) can be produced with properties ranging from soft films to rigid engineering plastics; thus, PE should be considered a class of materials rather than

a single polymer. These material properties depend largely on the type and distribution of branches along the polyethylene backbone. Thus, branching in polyethylene has been studied in great detail for more than 60 years [209–212]. Branch content of ethylene-based materials can be manipulated by mode of polymerization, but all polyethylenes produced by chain-addition polymerization contain some amount of random branching caused by chain-transfer events, and these branches have some distribution of length. ADMET offers an attractive method for producing branched polyethylene with precise branch identity and spacing along the PE backbone.

ADMET has thus far been directed towards modeling methyl-branched PE. These methyl-branched polymers can be construed as being polyethylene containing only methyl branching or as copolymers of ethylene and propylene. It is important to note that ADMET allows for control of short-chain branch (SCB) identity and branch distribution simply by appropriate monomer design. Modern metathesis catalysts promote ADMET in a very selective manner and consequently do not lead to side reactions that produce random branching, which is often observed for coordination polymerization catalysts. In fact, SCB and short-chain branch distribution (SCBD) affect material properties such as stiffness, tensile strength, processability, and softening [213]. These materials can be made in two ways: by homopolymerization of a methyl-branched diene to give a polymer with precisely spaced methyl branching [214] or by copolymerization of a methyl-branched diene and 1,9-decadiene to give a polymer with a statistical distribution of methyl branches along the polyethylene backbone (Scheme 3.9-59) [208].

Precisely spaced methyl-branched ADMET polyethylene seems to be a new class of polyethylene based on the properties of these materials [214]. Specifically, these polymers display dramatically sharper melting transitions at lower temperatures than any of the similar polyethylenes in the literature or in production, including ethylene-propylene copolymers with similar methyl branch content. In contrast, ADMET polyethylene with no branches melts similarly to commercial and other-



Scheme 3.9-59. ADMET synthesis of methyl-branched polyethylene with precise or statistical branch placement.

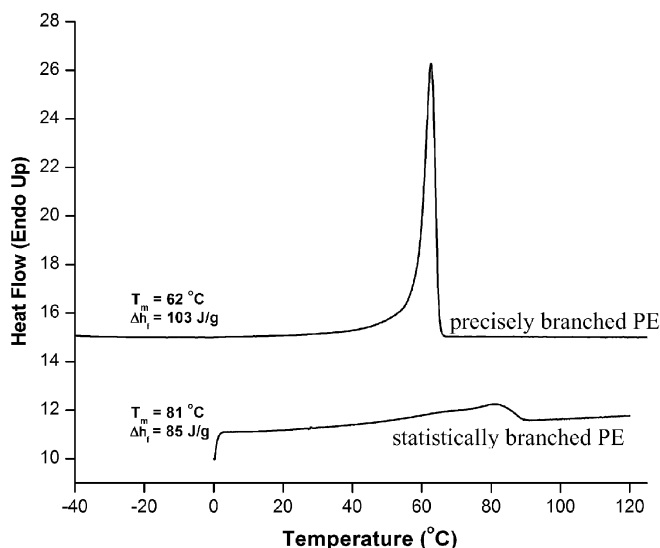


Fig. 3.9-5. DSC thermograms of precisely (46 methyl branches per 1000 carbons) and statistically (43 methyl branches per 1000 carbons) methyl-branched ADMET PE showing the distinctly different melting behavior of the two materials. Used with permission from ACS [208]

wise known samples. The morphology of the precisely methyl-branched materials has been further studied with various X-ray techniques [215], and the results concur with the notion that the precise spacing of the methyl branches imparts a special order to the material that previously had not been observed in polyethylene with similar branch content.

Copolymers of a methyl-branched diene with 1,9-decadiene, on the other hand, behave more like commercial or otherwise known polyethylenes in that the melting transitions are much broader than those of the precisely branched PE of similar branch content (Figure 3.9-5) [208]. The melting temperature and crystalline fraction of these polymers both smoothly decrease with increasing methyl branch content. A complete comparison of ADMET PE with commercial and otherwise known samples of PE is given in Table 3.9-5. ADMET copolymers containing lower propylene content display the expected orthorhombic crystal phase. However, ADMET copolymers containing more than ~10% propylene content were found to adopt a hexagonal crystal phase. This switch from orthorhombic to hexagonal crystal structure occurs at lower propylene content than any other known ethylene-propylene copolymers in the absence of external factors, such as temperature, pressure, and ionizing radiation.

The results so far have demonstrated the utility of the ADMET approach for modeling polyethylene produced by chain-addition techniques and contributed to the understanding of the molecular origins of the material properties of this important polymer. The high structural purity of the ADMET polymers differ-

Tab. 3.9-5. Comparison of the melting temperatures for various types of PE including precisely and statistically methyl-branched ADMET PE.

Type of PE	$10^3 M_n$	Methyl branches per 1000 carbons	T_m (°C)
Theoretical PE ^a	24–114	0	141.5–146.5
Metallocene PE ^b	30–1500	0.9–1.2	137–140
HDPE ^a	50–250	1–6	133–138
Brookhart PE ^c	14–65	1.2–74	97–132
Ethylene/propylene copolymers ^d	20–70	2–100	80–133
LDPE ^a	20–100	30–60	105–115
ADMET PE [199]	2–15	0	131–134
Precisely methyl-branched	17.5	100	–14
ADMET PE [214]	8.5	83	11
	17.1	63	39
	17.4	50	57
	72.0	50	57
	20.2	46	62
Statistically methyl-branched	13.7	56	52
ADMET PE [208]	30.5	43	81
	27.0	25	112
	26.2	14	119
	23.2	7.1	123
	15.3	1.5	129

^aHoffman, J. D. *Polymer* **1983**, 24, 3–26.^bKaminsky, W. *Macromol. Chem. Phys.* **1996**, 197, 3907.^cJohnson, L. K.; Killian, C. M.; Brookhart, M. J. *Am. Chem. Soc.* **1995**, 117, 6414.^dWunderlich, B.; Poland, D. J. *Polym. Sci. Polym. Chem.* **1963**, 1, 357.

entiate them from similar materials produced by chain or coordination polymerization and provides a unique opportunity to learn more about the structure-property relationships in polyethylene. Future efforts will be directed at modeling polyethylene with longer branches in both a random and statistical fashion.

3.9.11.3

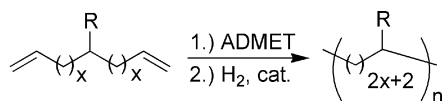
Functionalized Polyethylene

Functionalized polyethylene is a highly sought-after class of polymeric materials due to the desire to improve the adhesion, printability, and barrier properties of polyethylene [216]. Polyethylene can be functionalized after polymerization, but many research groups and commercial firms are seeking methods to directly copolymerize ethylene with polar monomers. This approach has been hindered historically by differences in reactivity of ethylene and polar monomers towards radical or other modes of chain polymerization. Consequently, the range of comonomer composition is restricted to a small range in many cases [217]. Differences

in reactivity can also lead to highly alternating microstructures. Direct copolymerization of ethylene and polar monomers also tends to produce highly branched polymers due to the same mechanisms that lead to branching in polyethylene.

Current work is focused on the direct copolymerization of ethylene and polar monomers by sophisticated transition metal catalysts. However, these catalysts often are stabilized by polar functional groups, thus hindering the polymerization. Among the examples of successful incorporation of functional vinyl comonomers into polyethylene with transition metal catalysts, functional groups tend to reside at the end of short branches and not directly in the main chain [216, 218], due to either separation of the functional group from the polymerizable olefin with methylene groups in the polar monomer or subtle details of the mechanism of the catalysis. For many applications, however, linear polymers with main-chain incorporation of functional groups are desired due to the material properties of linear polyethylene. ADMET provides a unique method of synthesizing completely linear polymers analogous to sequence-specific or statistical copolymers of ethylene and polar monomers in a wide variety of comonomer compositions.

The ADMET approach to these materials is to polymerize an appropriately functionalized diene, followed by selective hydrogenation of the backbone olefins (Scheme 3.9-60). A series of ethylene vinyl acetate copolymers was synthesized by ADMET and is novel in that all commercial copolymers of this kind are produced by radical polymerization under conditions similar to low density polyethylene (LDPE) and hence are highly branched [165]. ROMP of acetoxy-functionalized cyclooctene has also been used to synthesize linear copolymers of ethylene and vinyl acetate with higher vinyl acetate content, but these polymers are not sequence specific due to the asymmetry of the monomer. As is the case for precisely branched ADMET polyethylene, these ethylene vinyl acetate copolymers seem to adopt a unique morphology, characterized by sharp and relatively low melting points. Interestingly, the extrapolation of the plot of melting temperature versus vinyl acetate content to zero vinyl acetate content yields a predicted melting point of 145.6 °C, close to that predicted theoretically for high-molecular-weight linear polyethylene. These materials also display a peak in the WAXS spectra corresponding to the all-*trans* run length of the ethylene segments between the functional groups. Linear ethylene/acrylate ester copolymers were also synthesized by ADMET/hydrogenation, and their behavior is similar to the EVA copolymers [170]. Acrylate ester copolymers melt at slightly lower temperatures than the EVA copolymers with the same run length of methylene units between the functionalized carbons (Table 3.9-6).

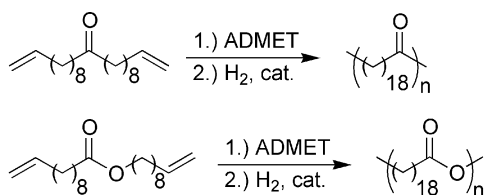


Scheme 3.9-60. ADMET synthesis of sequence-specific linear copolymers of ethylene and vinyl acetate, methyl acrylate, or ethyl acrylate.

Tab. 3.9-6. Melting points for sequence-specific copolymers of ethylene and polar comonomers.

R^a	γ^a	T_m (°C)
OAc	18	23
OAc	20	35
OAc	22	41
OAc	26	57
CO ₂ Me	18	14.4
CO ₂ Me	22	37
CO ₂ Et	18	12.5

^a Refers to the variable $2x + 2$ as shown in Scheme 3.9-60.



Scheme 3.9-61. ADMET synthesis of copolymers of ethylene with carbon monoxide or carbon dioxide. Orientation of ester groups along the polymer chain is disordered; HH, HT, and TT linkages are possible with a predicted ratio of 1:2:1.

This approach to functional polyethylene also was employed in the synthesis of ethylene/carbon dioxide and ethylene/carbon monoxide copolymers (Scheme 3.9-61) [219]. The carbon monoxide copolymers are particularly novel in that most copolymers of ethylene and carbon monoxide, although typically linear, are either alternating or have very low CO contents. These polymers displayed high melting points relative to the other precisely spaced functionalized polyethylene. The ketone-functionalized polyethylene displayed a melting point of 134 °C, approximately equal to that of ADMET polyethylene. This result was expected since the ketone moiety is known not to greatly perturb the crystal packing of polyethylene. The WAXS spectrum for the polyester displayed a peak corresponding to the all-*trans* run length of methylene units between the ester groups.

Copolymers of ethylene and styrene and ethylene and vinyl chloride were also prepared [170]. Due to the high reactivity of styrene compared to ethylene, copolymers of ethylene and styrene are traditionally unattainable, although there are now some examples of these polymers produced by metallocene catalysts or Ziegler-Natta polymerization. Since the phenyl group is large, the crystalline phase of the ADMET copolymer is highly perturbed and the copolymer melts at only −12 °C.

Tab. 3.9-7. Melting point of sequence-specific copolymers of ethylene and polar comonomers with 18 methylene groups separating the functionalized backbone carbons.

Functionality	T_m (°C)
Ph	−12
CO ₂ Et	13
CO ₂ Me	14
OMe	23
Me	57
Cl	77
=O	134

The chloride substituent on the other hand, is a relatively small pendant group and melts at 77 °C, 20 °C higher than the precisely methyl-substituted polymer with the same spacing between pendant groups (Table 3.9-7).

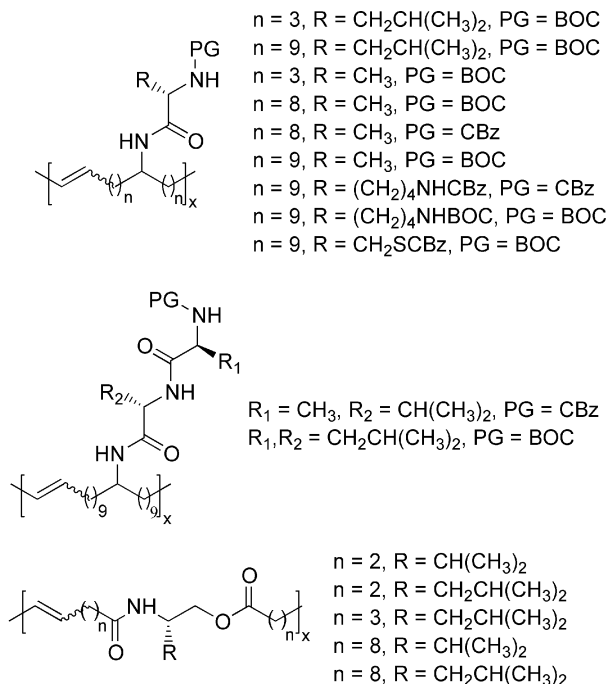
3.9.12

Towards Biologically Useful Polymers via ADMET

The recent advances in ruthenium olefin metathesis catalysts allow for the polymerization of more and more functionalized ADMET monomers. One application of these catalysts is the polymerization of amino acid and peptide-containing monomers for biological applications [150, 220]. RCM of an olefin-functionalized peptide was achieved with **[Ru]1** [221], but the high conversions required for ADMET were not achievable until the development of **[Ru]2**.

These chiral polyolefins are of interest for a variety of biomaterial applications such as proteomics and cell adhesion. Protected amino acids and sequences of amino acids can be incorporated into ADMET polymers either in the backbone or as pendant groups (Scheme 3.9-62). Many of the polymerizations required the use of THF, a coordinating solvent, to allow for high conversion. The resulting polymers have molecular weights similar to those of common polar condensation polymers such as nylon.

Some of these unsaturated materials are highly crystalline, and some are completely amorphous. Figure 3.9-6 shows the DSC thermogram of one of these materials. The material properties of these polymers are highly dependent on the nature of any protecting groups that may be present. Certain polymers can be cast into tough films with tensile modulus up to 220 MPa and elongation at break up to 260%. WAXS studies have shown that the crystalline samples exhibit order unlike polyethylene, but the exact nature of the crystal packing has not yet been determined.



Scheme 3.9-62. Mono-peptide, dipeptide, and amino alcohol-derived ADMET polymers.

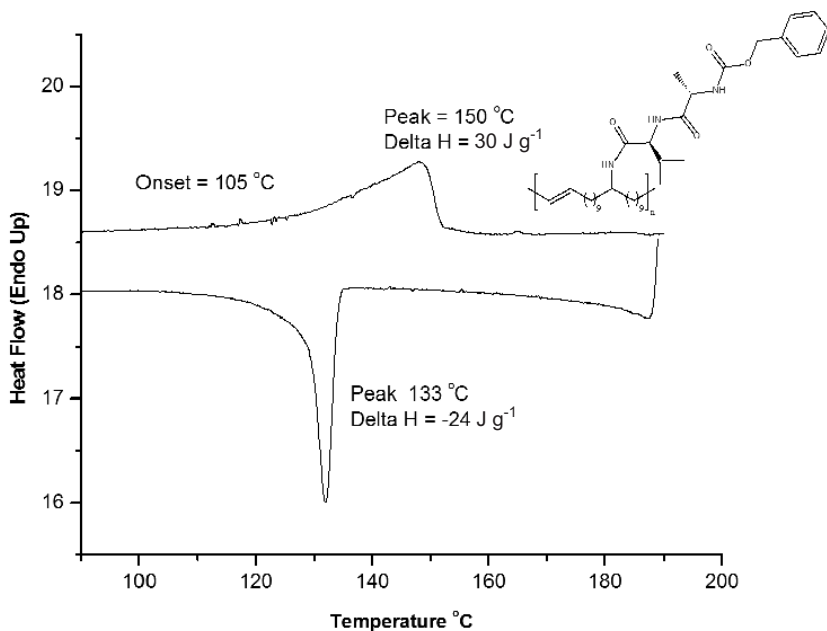


Fig. 3.9-6. DSC thermogram of a dipeptide-derived ADMET polymer. Used with permission from ACS [220]

3.9.13

Solid-State Polymerization

Solid-state polymerization (SSP) is a well-known phenomenon in the polycondensation community [222]. It involves polymerization of monomers or further polymerization of polymers in the solid state and is utilized for some polyesters and polyamides in large-scale production.

Results have shown that ADMET reactions with [Mo]2, [Ru]1, and [Ru]2 are capable of proceeding in the solid state, although it is not known whether the polymerization occurs wholly in amorphous phase or whether it occurs to some extent in or at the boundaries of crystalline phases [223]. So far, this phenomenon has been conclusively demonstrated only for the polymerization of 1,9-decadiene to polyoctenamer, which crystallizes once oligomers are formed. After crystallization, molecular weight growth continues in the semi-crystalline polymer for a period of days under a slow flow of inert gas or under vacuum. Normal catalyst loadings (500:1 monomer to catalyst ratio, for example) are employed in this chemistry. It is believed that operating in semi-rigid solid phase will prolong the lifetime of metathesis catalysts by preventing bimolecular decomposition of the ruthenium methyldiene complex and other decomposition pathways that occurs in the fluid liquid phase. Further work is aimed at determining the scope and applicability of solid-state metathesis polymerization and the feasibility of conducting RCM and CM reactions in the solid state.

3.9.14

Conclusions and Outlook

ADMET has been proven to be a general method of synthesizing unsaturated linear polymers with a variety of main-chain and pendant functionalities. The viability of this chemistry has been and will be dependent on new developments in metathesis catalyst synthesis. More robust catalysts are continually making ADMET more accessible to polymer chemists without specialized equipment or experience in handling sensitive organometallic complexes. Modeling of polyolefins and synthesis of biologically active polymers are two research areas for which this polymerization is useful and uniquely well suited. Overall, the possibilities for utilization of this polymerization reaction are vast and under-explored.

References

- 1 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*, 2nd Ed.; Academic Press: San Diego, CA, 1997, p. 1.
- 2 GRUBBS, R. H.; MILLER, S. J.; FU, G. C. *Acc. Chem. Res.* **1995**, 28, 446–452.
- 3 SCHUSTER, M.; BLECHERT, S. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2037–2056.
- 4 GRUBBS, R. H.; CHANG, S. *Tetrahedron* **1998**, 54, 4413–4450.
- 5 ARMSTRONG, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.

- 6 BLECHERT, S. *Pure Appl. Chem.* **1999**, 71, 1393–1399.
- 7 FURSTNER, A. *Angew. Chem., Int. Ed.* **2000**, 39, 3012–3043.
- 8 WRIGHT, D. L. *Curr. Org. Chem.* **1999**, 3, 211–240.
- 9 TENG, X.; CEFALO, D. R.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2002**, 124, 10779–10784.
- 10 DOLMAN, S. J.; SATTELY, E. S.; HOVEYDA, A. H.; SCHROCK, R. R. *J. Am. Chem. Soc.* **2002**, 124, 6991–6997.
- 11 BLACKWELL, H. E.; O'LEARY, D. J.; CHATTERJEE, A. K.; WASHENFELDER, R. A.; BUSSMANN, D. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2000**, 122, 58–71.
- 12 SMITH, A. B., III; ADAMS, C. M.; KOZMIN, S. A.; PAONE, D. V. *J. Am. Chem. Soc.* **2001**, 123, 5925–5937.
- 13 CHATTERJEE, A. K.; GRUBBS, R. H. *Org. Lett.* **1999**, 1, 1751–1753.
- 14 SESHADRI, H.; LOVELY, C. J. *Org. Lett.* **2000**, 2, 327–330.
- 15 MORGAN, J. P.; MORRILL, C.; GRUBBS, R. H. *Org. Lett.* **2002**, 4, 67–70.
- 16 LA, D. S.; FORD, J. G.; SATTELY, E. S.; BONITATEBUS, P. J.; SCHROCK, R. R.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, 121, 11603–11604.
- 17 SNAPPER, M. L.; TALLARICO, J. A.; RANDALL, M. L. *J. Am. Chem. Soc.* **1997**, 119, 1478–1479.
- 18 BUCHMEISER, M. R. *Chem. Rev.* **2000**, 100, 1565–1604.
- 19 SCHROCK, R. R. *Acc. Chem. Res.* **1990**, 23, 158–165.
- 20 MAUGHON, B. R.; GRUBBS, R. H. *Macromolecules*, **1997**, 30, 3459–3469.
- 21 SCHWENDEMAN, J. E.; CHURCH, C. A.; WAGENER, K. B. *Adv. Synth. Catal.* **2002**, 344, 597–613.
- 22 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997, Ch. 1.
- 23 *Ibid.* pp. 36–40.
- 24 *Ibid.* pp. 41–43.
- 25 *Ibid.* Ch. 17.
- 26 CALDERON, N.; OFSTEAD, E. A.; JUDY, W. A. *J. Polym. Sci. A-1* **1967**, 5, 2209–2217.
- 27 CALDERON, N.; SCOTT, K. W.; OFSTEAD, E. A. *Chim. Ind. (Milan)* **1970**, 52, 1169.
- 28 CALDERON, N.; CHEN, H. Y.; SCOTT, K. W. *Tetrahedron Lett.* **1967**, 3327–3329.
- 29 CALDERON, N.; OFSTEAD, E. A.; WARD, J. P.; JUDY, W. A.; SCOTT, K. W. *J. Am. Chem. Soc.* **1968**, 90, 4133–4140.
- 30 HERRISON, J.-L.; CHAUVIN, Y. N. *Makromol. Chem.* **1971**, 141, 161.
- 31 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997, Ch. 3.
- 32 GRUBBS, R. H.; HOPPIN, C. R. *J. Am. Chem. Soc.* **1979**, 101, 1499–1508.
- 33 KATZ, T. J.; MCGINNIS, J. J. *J. Am. Chem. Soc.* **1977**, 99, 1903–1912.
- 34 KATZ, T. J.; ROTHCHILD, R. J. *J. Am. Chem. Soc.* **1976**, 98, 2519–2526.
- 35 GRUBBS, R. H.; CARR, D. D.; HOPPIN, C.; BURK, P. L. *J. Am. Chem. Soc.* **1976**, 98, 3478–3483.
- 36 BILHOU, J. L.; BASSET, J. M. J. *Organomet. Chem.* **1977**, 132, 395–407.
- 37 DODD, H. T.; RUTT, K. J. *J. Mol. Catal.* **1988**, 47, 67–71.
- 38 OFSTEAD, E. A.; LAWRENCE, J. P.; SENYEK, M. L.; CALDERON, N. J. *J. Mol. Catal.* **1980**, 8, 227–242.
- 39 TANAKA, K.; MIYAKARA, K.; TANAKA, K. *Chem. Lett.* **1980**, 623–626.
- 40 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997, pp. 54–58.
- 41 HOWARD, T. R.; LEE, J. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1980**, 102, 6876–6878.
- 42 LEE, J. B.; GAJDA, G. J.; SCHAEFER, W. P.; HOWARD, T. R.; IKARIYA, T.; STRAUS, D. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1981**, 103, 7358–7361.
- 43 LEE, J. B.; OTT, K. C.; GRUBBS, R. H. **1982**, 104, 7491–7496.
- 44 STRAUS, D. A.; GRUBBS, R. H. *J. Mol. Catal.* **1985**, 28, 9–25.
- 45 GILLIOM, L. R.; GRUBBS, R. H. *Organometallics* **1986**, 5, 721–724.
- 46 GILLIOM, L. R.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1986**, 108, 733–742.
- 47 CRABTREE, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons: New York, NY, 1994, pp. 280–286.

- 48 SCHAEVERIEN, C. J.; DEWAN, J. C.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 2771–2773.
- 49 SCHROCK, R. R.; DePUE, R. T.; FELDMAN, J.; SCHAEVERIEN, C. J.; DEWAN, J. C.; LIU, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423–1435.
- 50 SCHROCK, R. R.; DePUE, R. T.; FELDMAN, J.; YAP, K. B.; YANG, D. C.; DAVIS, W. M.; PARK, L.; DiMARE, M.; SCHOFIELD, M.; ANHAUS, J.; WALBORSKY, E.; EVITT, E.; KRÜGER, C.; BETZ, P. *Organometallics* **1990**, *9*, 2262–2275.
- 51 MURDZEK, J. S.; SCHROCK, R. R. *Organometallics* **1987**, *6*, 1373–1374.
- 52 SCHROCK, R. R.; MURDZEK, J. S.; BAZAN, G. C.; ROBBINS, J.; DiMARE, M.; O'REGAN, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.
- 53 OSKAM, J. H.; FOX, H. H.; YAP, K. B.; McCONVILLE, D. H.; O'DELL, R.; LICHTENSTEIN, B. J.; SCHROCK, R. R. *J. Organomet. Chem.* **1993**, *459*, 185–198.
- 54 TOREKI, R.; SCHROCK, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 2448–2449.
- 55 TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
- 56 NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.*, **1992**, *114*, 3974–3975.
- 57 NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.
- 58 SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- 59 WU, Z.; NGUYEN, S. T.; GRUBBS, R. H.; ZILLER, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.
- 60 ARDUENGO III, A. J. *Acc. Chem. Res.* **1999**, *32*, 913–921.
- 61 HERRMANN, W. A.; KÖCHER, C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162–2187.
- 62 HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSEN, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.
- 63 WESKAMP, T.; SCHATTENMANN, W. C.; SPIEGLER, M.; HERRMANN, W. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2490–2493.
- 64 SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
- 65 SCHOLL, M.; LEE, C. W.; GRUBBS, R. H. *Org. Lett.* **1999**, *1*, 953–956.
- 66 BIELAWSKI, C. W.; GRUBBS, R. H. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2903–2906.
- 67 GARBER, S. B.; KINGSBURY, J. S.; GRAY, B. L.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- 68 KINGSBURY, J. S.; HARRITY, J. P. A.; BONITATEBUS, P. J., JR.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
- 69 DINGER, M. B.; MOL, J. C. *Adv. Synth. Catal.* **2002**, *344*, 671–677.
- 70 FÜRSTNER, A.; ACKERMANN, L.; GABOR, B.; GODDARD, R.; LEHMANN, C. W.; MYNOTT, R.; STELZER, F.; THIEL, O. R. *Chem. Eur. J.* **2001**, *7*, 3236–3253.
- 71 VAN VELDTHUIZEN, J. J.; GARBER, S. B.; KINGSBURY, J. S.; HOVEYDA, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955.
- 72 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, NY, 1991, Ch. 2.
- 73 *Ibid.* p. 56.
- 74 *Ibid.* pp. 83–90.
- 75 WAGENER, K. B.; NEL, J. G.; KONZELMAN, J.; BONCELLA, J. M. *Macromolecules* **1990**, *23*, 5155–5157.
- 76 WAGENER, K. B.; PUTS, R. D.; SMITH, JR., D. W. *Makromol. Chem., Rapid Commun.* **1991**, *12*, 419–425.
- 77 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, NY, 1991, pp. 73–77.
- 78 WAGENER, K. B.; SMITH, JR., D. W. *Macromolecules* **1991**, *24*, 6073–6078.
- 79 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997, pp. 227–232.
- 80 BIELAWSKI, C. W.; BENITEZ, D.; GRUBBS, R. H. *Science* **2002**, *297*, 2041–2044.
- 81 FÜRSTNER, A.; THIEL, O. R.; ACKERMANN, L.; SCHANZ, H. J.; NOLAN, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207.
- 82 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*;

- Academic Press: San Diego, CA, 1997, Ch. 6, 7.
- 83 DOYLE, G. J. *Catal.* **1973**, 30, 118–127.
 - 84 KAWAI, T.; YAMAZAKI, Y.; TAOKA, T. *J. Catal.* **1984**, 89, 452–461.
 - 85 NUBEL, P. O.; LUTMAN, C. A.; YOKELSON, H. B. *Macromolecules* **1994**, 27, 7000–7002.
 - 86 GRUBBS, R. H.; HOPPIN, C. R. *J. Am. Chem. Soc.* **1979**, 101, 1499–1508.
 - 87 GRUBBS, R. H.; SWETNICK, S. J. *Mol. Catal.* **1980**, 8, 25–36.
 - 88 HECKELSBERG, L. F. *Anal. Chem.* **1983**, 55, 398–400.
 - 89 LINDMARK-HAMBERG, M.; WAGENER, K. B. *Macromolecules* **1987**, 20, 2949–2951.
 - 90 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997, pp. 4–5.
 - 91 NUBEL, P. O.; LUTMAN, C. A.; YOKELSON, H. B. *Macromolecules* **1994**, 27, 7000–7002.
 - 92 GÓMEZ, F. J.; ABOUD, K. A.; WAGENER, K. B. *J. Mol. Catal. A Chem* **1998**, 133, 159–166.
 - 93 GÓMEZ, F. J.; MANAK, M. S.; ABOUD, K. A.; WAGENER, K. B. *J. Mol. Catal. A Chem.* **2000**, 160, 145–156.
 - 94 WAGENER, K. B.; BONCELLA, J. M.; NEL, J. G. *Macromolecules* **1991**, 24, 2649–2657.
 - 95 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997, p. 406.
 - 96 PATTON, J. T.; BONCELLA, J. M.; WAGENER, K. B. *Macromolecules* **1992**, 25, 3862–3867.
 - 97 BRZEZINSKA, K.; WOLFE, P. S.; WATSON, M. D.; WAGENER, K. B. *Macromol. Chem. Phys.* **1996**, 197, 2065–2074.
 - 98 SMITH, J. A.; LEHMAN, JR., S. E.; O'DONNELL, P. M.; WAGENER, K. B. unpublished results.
 - 99 LEHMAN, JR., S. E.; SCHWENDEMAN, J. E.; O'DONNELL, P. M.; WAGENER, K. B. *Inorg. Chim. Acta* accepted for publication.
 - 100 BOURGEOIS, D.; PANCRAZI, A.; NOLAN, S. P.; PRUNET, J. J. *Organomet. Chem.* **2002**, 643–644, 247–252.
 - 101 KINDERMAN, S. S.; VAN MAARSEVEEN, J. H.; SCHOEMAKER, H. E.; HIEMSTRA, H.; RUTJES, F. P. J. T. *Org. Lett.* **2001**, 3, 2045–2048.
 - 102 GINDELBERGER, D.; FELLOWS, I. M.; UNG, T. A.; PEDERSON, R. L. *Abstr. Pap. Am. Chem. Soc.* **2002**, 224, 222–ORGN.
 - 103 KATZ, T. J.; LEE, S. J.; ACTON, N. *Tetrahedron Lett.* **1976**, 4247–4250.
 - 104 KATZ, T. J.; ACTON, N. *Tetrahedron Lett.* **1976**, 4251–4254.
 - 105 DALL'ASTA, G.; MAZZANTI, G.; NATTA, G.; PORRI, L. *Makromol. Chem.* **1962**, 56, 224–227.
 - 106 NATTA, G.; DALL'ASTA, G.; PORRI, L. *Makromol. Chem.* **1965**, 81, 253.
 - 107 IVIN, K. J.; ROONEY, J. J.; BENCZE, L.; HAMILTON, J. G.; LAM, L. M.; LAPIENIS, G.; REDDY, B. S. R.; HO, H. T. *Pure Appl. Chem.* **1982**, 54, 447–460.
 - 108 DEFIGUEIRDO, C. M. C.; GOMES, A. de S. J. *Polym. Sci., Polym. Chem.* **1979**, 17, 2633–2637.
 - 109 IVIN, K. J.; LAPIENIS, G.; ROONEY, J. J. *Polymer* **1980**, 21, 367–369.
 - 110 BRANDRUP, J.; IMMERGUT, E. H. *Polymer Handbook*; John Wiley & Sons: New York, 1975; Section V-I.
 - 111 TALLARICO, J. A.; BONITATEBUS, JR., P. J.; SNAPPER, M. L. *J. Am. Chem. Soc.* **1997**, 119, 7157–7158.
 - 112 WAGENER, K. B.; KONZELMAN, J. *Polym. Prepr.* **1991**, 32, 375–376.
 - 113 KONZELMAN, J.; WAGENER, K. B. *Macromolecules* **1995**, 28, 4686–4692.
 - 114 KONZELMAN, J. Ph.D. Dissertation, University of Florida, 1993.
 - 115 STEIGER, D.; TERVOORT, T.; WEDER, C.; SMITH, P. *Macromol. Rapid Commun.* **2000**, 21, 405–422.
 - 116 KATZ, T. J.; MCGINNIS, J.; ALTUS, L. *J. Am. Chem. Soc.* **1976**, 98, 606–608.
 - 117 TAO, D. Ph.D. Dissertation, University of Florida, 1993.
 - 118 SANFORD, M. S.; LOVE, J. A.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, 123, 6543–6554.
 - 119 ROSSINI, F. D.; PITZER, K. S.; ARNETT, R. L.; BRAUN, R. M.; PIMENTEL, G. C. *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*; Carnegie-Mellon

- University Press: Pittsburgh, PA, 1953.
- 120 KONZELMAN, J.; WAGENER, K. B. *Macromolecules* **1996**, *29*, 7657–7660.
 - 121 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, NY, 1991, pp. 141–150.
 - 122 *Ibid.* Ch. 6.
 - 123 O'DONNELL, P. M.; BRZEZINSKA, K. R.; POWELL, D.; WAGENER, K. B. *Macromolecules* **2001**, *34*, 6845–6849.
 - 124 O'DONNELL, P. M.; WAGENER, K. B. submitted for publication.
 - 125 SHIRIKAWA, H. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2574–2580.
 - 126 CHIEN, C. W. *Polyacetylene: Chemistry, Physics, and Material Science*; Academic Press, Inc. Ltd.: London, U.K., pp. 46–47.
 - 127 TAO, D.; WAGENER, K. B. *Macromolecules* **1994**, *27*, 1281–1283.
 - 128 BURROUGHS, J. H.; BRADLEY, D. D. C.; BROWN, A. R.; MARKS, R. N.; MAVKAY, K.; FRIEND, R. H.; BURNS, P. L.; HOLMES, A. B. *Nature* **1990**, *347*, 539–541.
 - 129 WESSLING, R. A. J. *Polym. Chem. Polym. Symp.* **1985**, *72*, 55–66.
 - 130 CONTICELLO, V. P.; GIN, D. L.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 9708–9711.
 - 131 JANG, M. S.; SONG, S. Y.; LEE, J.-I.; SHIM, H.-K.; ZYUNG, T. *Macromol. Chem. Phys.* **1999**, *200*, 1101–1106.
 - 132 PANG, Y.; LI, J.; HU, B.; KARASZ, F. E. *Macromolecules* **1999**, *32*, 3946–3950.
 - 133 AHN, T.; JANG, M. S.; SHIM, H. K.; HWANG, D. H.; ZYUNG, T. *Macromolecules* **1999**, *32*, 3279–3285.
 - 134 WINKLER, B.; TASCH, S.; ZOJER, E.; UNGERANK, M.; LEISLING, G.; STELZER, F. *Synth. Met.* **1996**, *83*, 177–180.
 - 135 WAGAMAN, M. W.; GRUBBS, R. H. *Macromolecules* **1997**, *30*, 3978–3985.
 - 136 THORN-CSÁNYI, E.; KRAXNER, P. *Macromol. Chem., Rapid Commun.* **1995**, *16*, 147–153.
 - 137 BAZAN, G. C.; MIAO, Y.-J.; RENAK, M. L.; SUN, B. J. *J. Am. Chem. Soc.* **1996**, *118*, 2618–2624.
 - 138 FOX, H. H.; SCHROCK, R. R.; O'DELL, R. *Organometallics* **1994**, *13*, 635–639.
 - 139 OAKLEY, G.; LEHMAN, JR., S. E.; WAGENER, K. B. unpublished results.
 - 140 MÜLLNER, R.; WINKLER, B.; STELZER, F.; TASCH, S.; HOCHFILZER, C.; LEISLING, G. *Synthetic Metals* **1999**, *105*, 129–133.
 - 141 SCHLICK, H.; STELZER, F.; TASCH, S.; LEISLING, G. *J. Mol. Catal. A: Chem.* **2000**, *160*, 71–84.
 - 142 THORN-CSÁNYI, E.; PFLUG, K. P. *Makromol. Chem., Rapid Commun.* **1993**, *14*, 619–624.
 - 143 THORN-CSÁNYI, E.; PFLUG, K. P. *J. Mol. Catal.* **1994**, *90*, 29–37.
 - 144 THORN-CSÁNYI, E.; KRAXNER, P. *J. Mol. Catal. A: Chem.* **1997**, *115*, 21–28.
 - 145 THORN-CSÁNYI, E.; KRAXNER, P.; STRACHOTA, A. *Macromol. Rapid Commun.* **1998**, *19*, 223–228.
 - 146 NOMURA, K.; MORIMOTO, H.; IMANISHI, Y.; RAMHANI, Z.; GEERTS, Y. *J. Polymer Sci.: Part A: Polym. Chem.* **2001**, *39*, 2463–2470.
 - 147 MIAO, Y.-J.; BAZAN, G. C. *Macromolecules* **1997**, *30*, 7414–7418.
 - 148 TSUIE, B.; WAGENER, K. B.; REYNOLDS, J. R. *Polym. Prepr.* **1999**, *40*, 790.
 - 149 KAWAI, T.; SHIGA, K.; IYODA, T. *J. Mol. Catal. A Chem.* **2000**, *160*, 173–179.
 - 150 HOPKINS, T. E.; PAWLOW, J. H.; KOREN, D. L.; DETERS, K. S.; SOLIVAN, S. M.; DAVIS, J. A.; GÓMEZ, F. J.; WAGENER, K. B. *Macromolecules* **2001**, *34*, 7920–7922.
 - 151 FURSTNER, A.; THIEL, O. R.; LEHMANN, C. W. *Organometallics* **2002**, *21*, 331–335.
 - 152 FELDMAN, J.; MURDZEK, J. S.; DAVIS, W. M.; SCHROCK, R. R. *Organometallics* **1989**, *8*, 2260–2265.
 - 153 BRZEZINSKA, K.; WAGENER, K. B. *Macromolecules* **1991**, *24*, 5273–5277.
 - 154 BRZEZINSKA, K.; WAGENER, K. B. *Macromolecules* **1992**, *25*, 2049–2052.
 - 155 WAGENER, K. B.; BRZEZINSKA, K.; BAUCH, C. G. *Makromol. Chem., Rapid Commun.* **1992**, *13*, 75–81.
 - 156 BRZEZINSKA, K.; DILOCKER, S.; WAGENER, K. B. *Polym. Prepr.* **1996**, *37*, 279–280.
 - 157 VALENTI, D. J.; WAGENER, K. B. *Macromolecules* **1998**, *31*, 2764–2773.
 - 158 HOPKINS, T. E.; WAGENER, K. B. unpublished results.

- 159 ALLCOCK, H. R.; KELLAM, III, E. C. *Macromolecules* **2002**, 35, 40–47.
- 160 WOLFE, P. S.; WAGENER, K. B. *Macromolecules* **1999**, 32, 7961–7967.
- 161 O'GARA, J. E.; PORTMESS, J. D.; WAGENER, K. B. *Macromolecules* **1993**, 26, 2837–2841.
- 162 WAGENER, K. B.; BRZEZINSKA, K.; ANDERSON, J. D.; YOUNKIN, T. R.; STEPPE, K.; DEBOER, W. *Macromolecules* **1997**, 30, 7363–7369.
- 163 BAUCH, C. G.; WAGENER, K. B.; BONCELLA, J. M. *Makromol. Chem., Rapid Commun.* **1991**, 12, 413–417.
- 164 WATSON, M. D.; WAGENER, K. B. *Macromolecules* **2000**, 33, 3196–3201.
- 165 WATSON, M. D.; WAGENER, K. B. *Macromolecules* **2000**, 33, 5411–5417.
- 166 JOO, S. H.; YUN, Y.-K.; JIN, J.-I.; KIM, D. C.; ZIN, W.-C. *Macromolecules* **2000**, 33, 6704–6712.
- 167 WAGENER, K. B.; PATTON, J. T. *Macromolecules* **1993**, 26, 249–253.
- 168 FORBES, M. D. E.; PATTON, J. T.; MYERS, T. L.; MAYNARD, H. D.; SMITH, JR., D. W.; SCHULTZ, G. R.; WAGENER, K. B. *J. Am. Chem. Soc.* **1992**, 114, 10978–10980.
- 169 WAGENER, K. B.; PATTON, J. T.; FORBES, M. D. E.; MYERS, T. L.; MAYNARD, H. D. *Polym. Int.* **1993**, 32, 411–415.
- 170 WATSON, M. D.; WAGENER, K. B. *Macromolecules* **2000**, 33, 8963–8970.
- 171 SMITH, JR., D. W.; WAGENER, K. B. *Macromolecules* **1993**, 26, 1633–1642.
- 172 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, NY, 1991, pp. 582–582.
- 173 BRZEZINSKA, K. R.; SCHITTER, R.; WAGENER, K. B. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, 38, 1544–1550.
- 174 PAWLENKO, S. *Organosilicon Chemistry*; de Gruyter: Berlin, 1986; p. 14.
- 175 CUMMINGS, S. K.; SMITH, JR., D. W.; WAGENER, K. B. *Macromol. Rapid Commun.* **1995**, 16, 347–355.
- 176 CHURCH, C. A.; PAWLOW, J. H.; WAGENER, K. B. *Macromolecules* **2002**, 35, 5746–5751.
- 177 WOLFE, P. S.; GÓMEZ, F. J.; WAGENER, K. B. *Macromolecules* **1997**, 30, 714–717.
- 178 GÓMEZ, F. J.; WAGENER, K. B. *Polym. Prepr.* **1998**, 39, 540–541.
- 179 GÓMEZ, F. J.; WAGENER, K. B. *J. Organomet. Chem.* **1999**, 592, 271–277.
- 180 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997, Ch. 16.
- 181 WATSON, M. D.; WAGENER, K. B. *J. Polym. Sci. A: Polym. Chem.* **1999**, 37, 1857–1861.
- 182 WATSON, M. D.; WAGENER, K. B. *Macromolecules* **2000**, 33, 1494–1496.
- 183 CRAIG, S. W.; MANZER, J. A.; COUGHLIN, E. B. *Macromolecules* **2001**, 34, 7929–7931.
- 184 GOETHALS, E. J., Ed. *Telechelic Polymers: Synthesis and Applications*; CRC Press, Inc. Boca Raton, FL, 1989.
- 185 BOUTEVIN, B. *Adv. Polym. Sci.* **1991**, 94, 69.
- 186 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, NY, 1991, p. 146.
- 187 MARMO, J. C.; WAGENER, K. B. *Macromolecules* **1993**, 26, 2137–2138.
- 188 MARMO, J. C.; WAGENER, K. B. *Macromolecules* **1995**, 28, 2602–2606.
- 189 SCOTT, K. W.; CALDERON, N.; OFSTEAD, E. A.; JUDY, W. A.; WARD, J. P. *J. Am. Chem. Soc. Adv. Chem. Ser.* **1969**, 91, 399.
- 190 SCHWENDEMAN, J. E. Ph.D. Dissertation, University of Florida, 2002.
- 191 TAO, D.; WAGENER, K. B. *Polym. Prepr.* **1993**, 34, 469–470.
- 192 KONZELMAN, J.; WAGENER, K. B. *Macromolecules* **1995**, 28, 4686–4692.
- 193 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, NY, 1991, pp. 45–56.
- 194 CAVALLO, L. *J. Am. Chem. Soc.* **2002**, 124, 8965–8973.
- 195 HILLMYER, M. A.; LAREDO, W. R.; GRUBBS, R. H. *Macromolecules* **1995**, 28, 6311–6316.
- 196 LEHMAN, JR., S. E.; WAGENER, K. B. *Macromolecules* **2002**, 35, 48–53.
- 197 COURCHAY, F.; SWORN, J. C.; WAGENER, K. B. Unpublished results.
- 198 HAHN, S. F. *J. Polym. Sci., Part A* **1992**, 30, 397–408.
- 199 O'GARA, J. E.; WAGENER, K. B.; HAHN, S. F. *Makromol. Chem., Rapid Commun.* **1993**, 14, 657–662.

- 200 SCHWENDEMANN, J. E. Ph.D. Dissertation, University of Florida, 2002.
- 201 McLAIN, et al. *Proc. Am. Chem. Soc.: Div. Polym. Mater. Sci. Eng.* **1997**, 76, 264–265.
- 202 EVANS, S.; OSBORN, J. A.; JARDINE, F. H.; WILKINSON, G. *Nature* **1965**, 208, 1203–1204.
- 203 HALLMANN, P. S.; EVANS, S.; OSBORN, J. A.; WILKINSON, G. *Chem. Commun.* **1967**, 7, 305–306.
- 204 HALLMANN, P. S.; MCGARVEY, B. R.; WILKINSON, G. *J. Chem. Soc. A* **1968**, 3143–3150.
- 205 DROUIN, S. D.; ZAMANIAN, F.; FOGG, D. E. *Organometallics* **2001**, 20, 5495–5497.
- 206 LOUIE, J.; BIELAWSKI, C. W.; GRUBBS, R. H. *J. Am. Chem. Soc.* **2001**, 123, 11312–11313.
- 207 JARDINE, F. H.; SHERIDAN, P. S. In *Comprehensive Coordination Chemistry*; WILKINSON, G.; GILLARD, R. D.; MCLEVERTY, J. A., Eds.; Pergamon Press: Oxford, U.K., 1987, p. 901.
- 208 SWOREN, J. C.; SMITH, J. A.; WAGENER, K. B.; BAUGH, L. S.; RUCKER, S. P. *J. Am. Chem. Soc.* **2003**, 125, 2228–2240.
- 209 ALAMO, R. G.; VIERS, B. D.; MANDELKERN, L. *Macromolecules* **1993**, 26, 5740–5747.
- 210 GERUM, W.; HOHNE, G. W. H.; WILKE, W.; ARNOLD, M.; WEGNER, T. *Macromol. Chem. Phys.* **1995**, 196, 3797–3811.
- 211 GERUM, W.; HOHNE, G. W. H.; WILKE, W.; ARNOLD, M.; WEGNER, T. *Macromol. Chem. Phys.* **1995**, 197, 1691–1712.
- 212 ALAMO, R. G.; MANDELKERN, L.; STACK, G. M.; KRÖNKE, C.; WEGNER, G. *Macromolecules* **1994**, 27, 147–156.
- 213 SUN, T.; BRANT, P.; CHANCE, R. R.; GRAESSLEY, W. W. *Macromolecules* **2001**, 34, 6812–6820.
- 214 SMITH, J. A.; BRZEZINSKA, K. R.; VALENTI, D. J.; WAGENER, K. B. *Macromolecules* **2000**, 33, 3781–3794.
- 215 SMITH, J. A. Ph.D. Dissertation, University of Florida, 2002.
- 216 BOFFA, L. S.; NOVAK, B. M. *Chem. Rev.* **2000**, 100, 1479–1494.
- 217 ODIAN, G. *Principles of Polymerization*; John Wiley & Sons: New York, NY, 1991, Ch. 4.
- 218 TEMPEL, D. J.; JOHNSON, L. K.; HUFF, R. L.; WHITE, P. S.; BROOKHART, M. *J. Am. Chem. Soc.* **2000**, 122, 6686–6700.
- 219 WATSON, M. D.; WAGENER, K. B. *Macromolecules* **2000**, 33, 3196–3201.
- 220 HOPKINS, T. E.; WAGENER, K. B. *Macromolecules* **2003**, 36, 2206–2214.
- 221 MILLER, S. J.; BLACKWELL, H. E.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1996**, 118, 9606–9614.
- 222 SHI, C. M.; GROSS, S. M.; DESIMONE, J. M.; KISEROW, D. J.; ROBERTS, G. W. *Macromolecules* **2001**, 34, 2060–2064.
- 223 OAKLEY, G.; LEHMAN, JR., S. E.; SMITH, J. A.; VAN GERVER, P.; WAGENER, K. B. *Macromolecules* **2003**, 36, 539–542.

3.10

Acyclic Diyne Metathesis Utilizing *in Situ* Transition Metal Catalysts: An Efficient Access to Alkyne-Bridged Polymers

Uwe H. F. Bunz

Dedicated to K. Peter C. Vollhardt

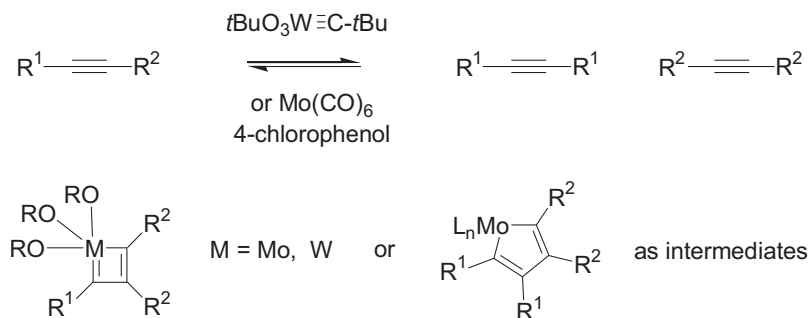
3.10.1

Introduction

Transition metals play a prominent role in the synthesis of polymers. Their applications range from Ziegler-Natta-type titanium, zirconium, and hafnium catalysts to soft late transition metal complexes [1]. In the synthesis of conjugated polymers, transition metal catalysts may be even more popular, and C–C single-bond-forming reactions as well as alkene metathesis have been utilized to make polyphenylenes, polyfluorenes, poly(phenylenevinylene)s (PPV), poly(phenyleneethynylene)s (PPE), polythiophenes, polyfuranes, poly(thiazole)s, polyacetylenes, and many other conjugated polymers [2–9]. In most cases, molecularly defined catalysts are utilized that operate in a mechanistically transparent fashion to accomplish polymer synthesis.

In this chapter “*in situ*” catalysts are examined. These are exploited in the acyclic diyne metathesis (ADIMET) of suitable diynes to give poly(aryleneethynylene)s (PAEs) and their model compounds. Due to the scope and limitations of this review, alkyne polymerization [10] and alkene metathesis with “classic” catalysts are not treated, even though some recent publications by Weder [11a] Wagener [11b] and others demonstrate that valuable, structurally defined materials are obtained [12]. Typical examples of *in situ* metathesis catalysts include, but are not restricted to, Mo(CO)_6 , W(CO)_6 , MoOCl_4 , and WOCl_4 , etc., combined with activators and/or reducing agents. This contribution will not cover the development alkyne metathesis has experienced by the use of the Schrock carbyne complexes [13] and the molybdenum-based catalysts developed by Fürstner [14] and Cummins [15], which are treated elsewhere in this book [14b].

The *in situ* ADIMET approach to the synthesis of conjugated oligomers and polymers of the PAE type is simple and powerful; it uses catalyst precursors (Mo(CO)_6 , phenols) that are air and water stable and commercially available at low cost. The catalysts form by a “shake and bake” process from these precursors during the metathesis reaction.



Scheme 3.10-1. General concept of alkyne metathesis.

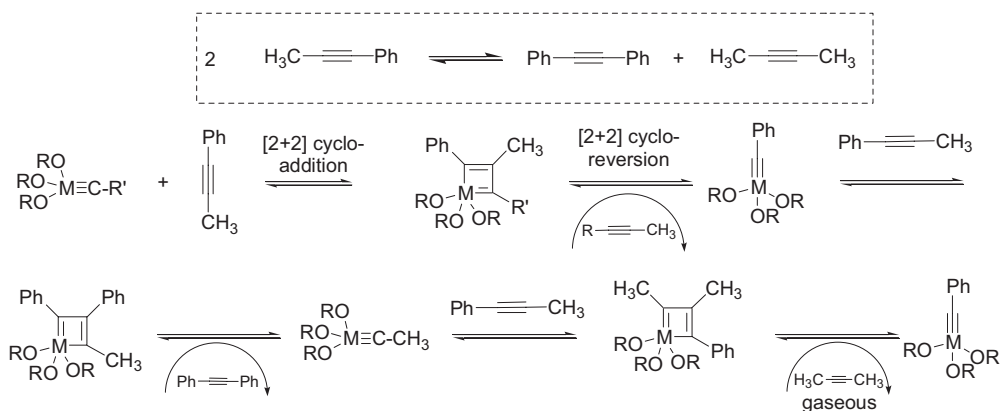
3.10.1.1

Alkyne Metathesis

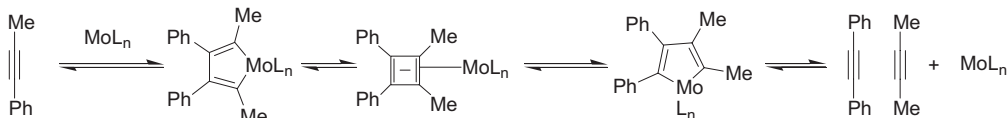
Alkyne metathesis is the scrambling of alkyne substituents (Scheme 3.10-1). Internal alkynes undergo this process efficiently, while terminal alkynes are polymerized under conditions successful for alkyne metathesis [10]. During alkyne metathesis a formal scission of the C–C triple bond and random reconnection occurs. A metallacyclobutadiene, a metallacyclopentadiene, or a cyclobutadiene complex is a possible intermediate according to mechanistic studies and/or product analysis.

Alkyne metathesis in homogeneous solution was discovered by Mortreux and Blanchard when they treated 4-methyltolane with a mixture of Mo(CO)_6 and resorcinol in a pressure tube at high temperature [18]. The authors detected a mixture of tolane, 4,4'-dimethyltolane and the starting 4-methyltolane and concluded that alkyne metathesis must have taken place under these conditions. Based on Mortreux's discovery, Villemin reported in 1982 that mixtures of Mo(CO)_6 and 4-chlorophenol are active in the alkyne metathesis and work considerably better than the original catalysts, perhaps due to the increased acidity of 4-chlorophenol compared to that of resorcinol or phenol itself [19]. In an extension of this work, Villemin reported that not only phenols but also silanols (Si–OH-containing compounds) activate Mo(CO)_6 , particularly if alkyne metathesis is conducted under microwave irradiation [20]. Mori examined the preparative value of the *in situ* alkyne metathesis catalysts for the synthesis of symmetrically and unsymmetrically substituted tolanes from propynylbenzenes. She used Villemin's simple catalysts to demonstrate that alkyne metathesis is a useful tool for organic synthesis. While the yields of her reactions were not always high, the simplicity of the method offers potential for a broad application.

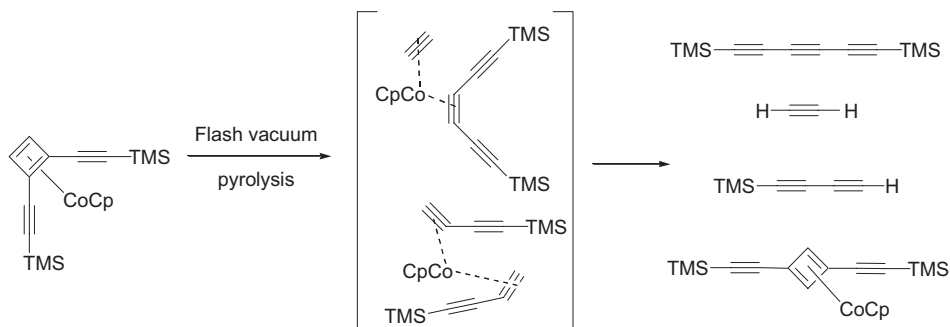
None of the early contributors to alkyne metathesis performed convincing mechanistic work until Vollhardt pyrolyzed a diethynylated cyclobutadiene complex in the gas phase (Scheme 3.10-4). The isolation of a mixture of three alkynes proved that the cycloreversion of the 4-membered ring, i.e., alkyne metathesis, had occurred – a viable mechanism for alkyne metathesis [17]. This formal mechanistic



Scheme 3.10-2. Mechanistic concept of alkyne metathesis via a carbyne complex according to Schrock [13], demonstrated at the example of metathesis of propynylbenzene.



Scheme 3.10-3. Mechanistic concept of alkyne metathesis via a metallacyclopentadiene as suggested by Mori [16].



Scheme 3.10-4. Mechanistic concept of alkyne metathesis via a cyclobutadiene complex as suggested by Vollhardt [17].

proof of alkyne metathesis was largely overlooked, but the idea was picked up by Mori, who explained alkyne metathesis with mixtures of 4-chlorophenol and $\text{Mo}(\text{CO})_6$ in terms of formation of an intermediate metallacyclopentadiene complex participating in a series of cycloadditions and cycloreversions (Scheme 3.10-3). To support her hypothesis, she demonstrated that the catalysts generated from $\text{Mo}(\text{CO})_6$ and 4-chlorophenol not only are active in alkyne metathesis but also promote alkyne trimerization to form substituted benzenes [21].

Alkyne trimerization with simple *in situ* catalysts is successful only if (1) heteroatoms are present in the substrate and (2) at least two of the three necessary alkynes are linked together [21]. This significant finding raises the question of whether *in situ* catalysts will always produce some cyclotrimerization products. Pschirer and Bunz [22] investigated alkyne metathesis of *ortho*-alkyl substituted propynylbenzenes. The yield of alkyne metathesis-induced dimerization is almost quantitative for these substrates. If cyclotrimerized materials had formed, their amount could have only been minute. This is vitally important for the use of simple catalysts in polymer formation; if benzene derivatives, side products of trimerization, form, cross-linking would lead to insoluble and uncharacterizable materials.

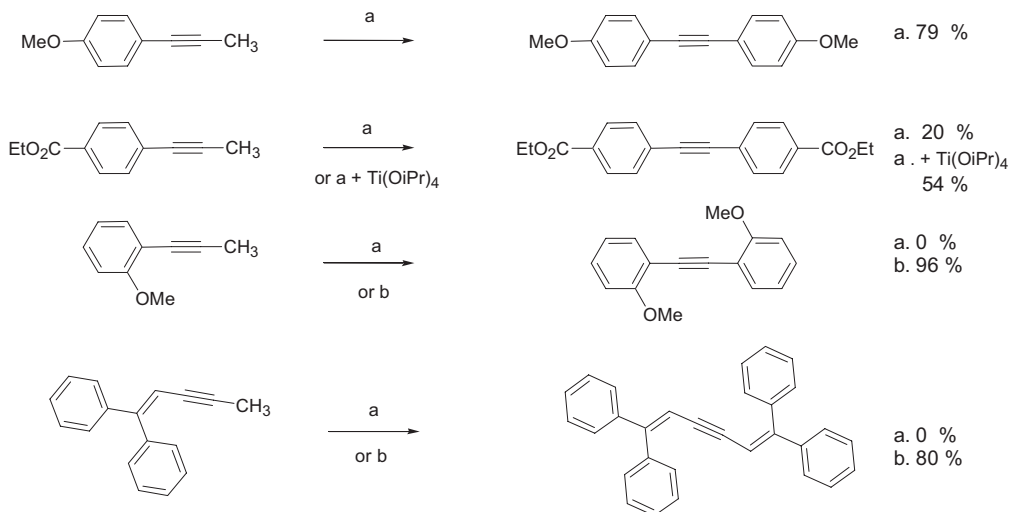
Regardless of whether defined carbyne complexes or *in situ* systems are discussed, the major mechanistic insights into the process of alkyne metathesis were provided by Schrock [13]. He prepared high oxidation state molybdenum and tungsten-carbyne complexes of the general structure $(RO)_3M\equiv C-R'$ ($M = Mo, W$) that are alkyne metathesis active. He demonstrated that alkyne metathesis with these carbyne complexes proceeds via a series of [2+2] cycloaddition and cycloreversion steps that lead to the split of internal alkynes via metallacyclobutadiene intermediates (Scheme 3.10-2). The Schrock mechanism can explain the catalytic activity of the *in situ* catalysts (from $Mo(CO)_6$ and 4-chlorophenol) as long as a small amount of oxidant is present that could transform the carbonyl complex into a molybdenum species of higher oxidation state. In the presence of both the phenol and the alkyne, a carbyne complex could form. The observation that dimolybdenum tetraacetate catalyzes alkyne metathesis [20] in the presence of phenols supports the carbyne mechanism, even though the operation of the Vollhardt-Mori [16, 17] mechanism cannot be excluded for the *in situ* catalysts until more mechanistic work is executed.

A problem encountered with the *in situ* catalysts is their relative sensitivity towards heteroatoms. In the presence of *meta*- and *para*-alkoxy groups, dimerization works fine when utilizing mixtures of $Mo(CO)_6$ and 4-chlorophenol; in the case of enynes or *ortho*-alkoxy-substituted propynylarenes, metathesis yields with these catalysts are close to zero. This drawback significantly decreases the usefulness of the *in situ* catalysts for synthetic applications. The catalytic activity increases if the *in situ* catalyst system is pre-activated (see Scheme 3.10-5b) by addition of hexyne. Enyne substrates and *ortho*-alkoxypropynylbenzenes dimerize in excellent yields [23] under those conditions.

3.10.2

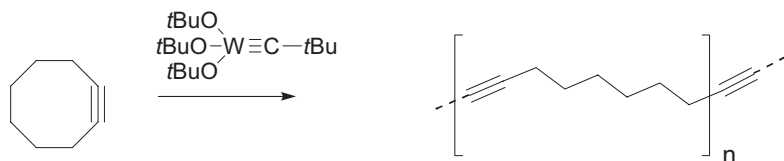
ADIMET: Synthesis of Alkyne-Bridged Polymers

The first use of alkyne metathesis for polymer formation was reported in 1988 by Schrock and Krouse [24], who treated cyclooctyne with a tungsten carbyne and obtained a polyoctynamer (Scheme 3.10-6). While the polymerization was apparently not living, it was a demonstration that alkyne metathesis is useful in polymer

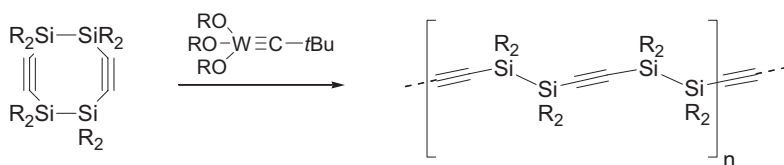


Scheme 3.10-5. Alkyne metathesis with two simple catalyst systems. Catalyst system (a) $\text{Mo(CO)}_6/4\text{-chlorophenol}$ 140°C in *ortho*-dichlorobenzene [22]. (b) “Super” *in situ*

catalyst system [23]: Pre-treat $\text{Mo(CO)}_6/4\text{-chlorophenol}$ and 3-hexyne at 140°C in a pressure tube, cool to 25°C , add monomer, and heat to 140°C for 2–24 h.

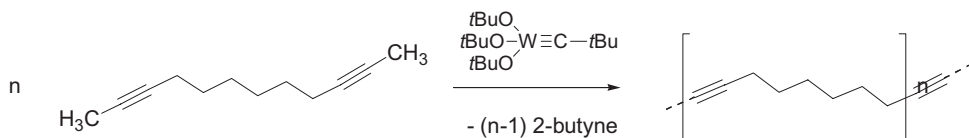


Scheme 3.10-6. Schrock's ROMP of cyclooctyne to polyoctynamer [24].

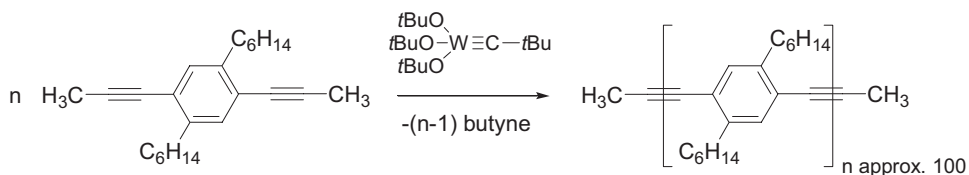


Scheme 3.10-7. Bazan's ROMP of a tetrasilacyclooctadiyne [25].

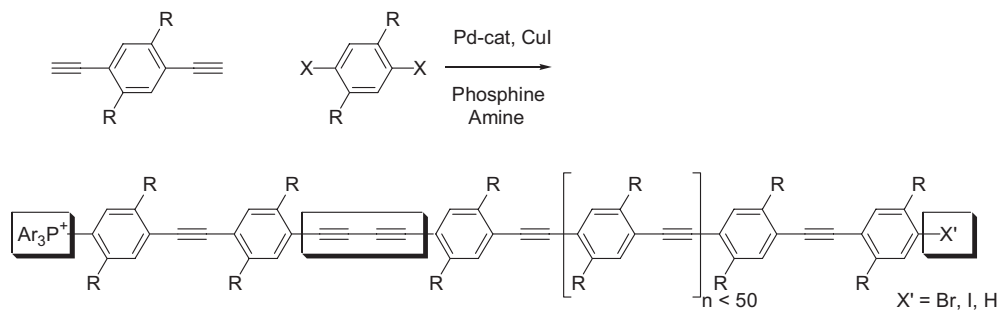
synthesis. In 1994 Bazan [25] described an interesting poly-(silane-alkynylene) by successful ring opening of a tetrasilacyclooctadiyne derivative (Scheme 3.10-7). These contributions did not get their well-deserved and appropriate recognition. In 1997 Weiss et al. examined the acyclic diyne metathesis (ADIMET) of decadiyne utilizing a Schrock tungsten-carbyne complex [26]. The authors found that a polyoctynamer (Scheme 3.10-8) forms in good yield and with a satisfactory degree of polymerization (P_n). In the same contribution the authors showed that dipropynylated benzenes metathesize under these conditions to give a soluble poly(*paraphenyleneethynylene*) (PPE, Scheme 3.10-9) in 70% yield and with a



Scheme 3.10-8. Weiss's ADIMET of 2,9-decadiyne to polyoctynamer [26].



Scheme 3.10-9. Weiss's, Bunz's, and Müllen's ADIMET route to poly(*paraphenyleneethynylene*)s [26].



Scheme 3.10-10. Pd-catalyzed coupling reactions of the Heck-Cassar-Sonogashira type.

degree of polymerization (P_n) of approximately 100 repeating units. PPEs could be made by ADIMET; the recorded P_n was immediately competitive with the hitherto reported PPEs obtained by Pd-catalyzed couplings of the Heck-Cassar-Sonogashira type. The popular Pd-catalyzed couplings produce PPEs that are plagued by defects (Scheme 3.10-10). The occurrence of diynes in the polymer backbone is promoted by catalyst activation and/or by the presence of traces of oxygen or other oxidizing agents. Pd-catalyzed dehalogenation and phosphonium salt formation lead to polymers with ill-defined end groups [27]. The Pd-catalyzed reactions are polycondensations of the AA + BB type, in which a slightly imbalanced stoichiometry leads to a significant decrease in molecular weight. As a consequence, the development of a new, powerful yet simple synthetic approach to PPEs of high molecular weight and purity was desirable. Acyclic diyne metathesis (ADIMET) appeared to be ideal, and was not clear why the synthesis of alkyne-bridged polymers by metathesis methods had been neglected so far. The structures that can be formed are exciting and of interest as optoelectronic and sensory materials [25, 26]. The prerequisite Schrock carbyne complexes, so useful for ADIMET, are not commercially available and require a significant investment of time and effort. Thus,

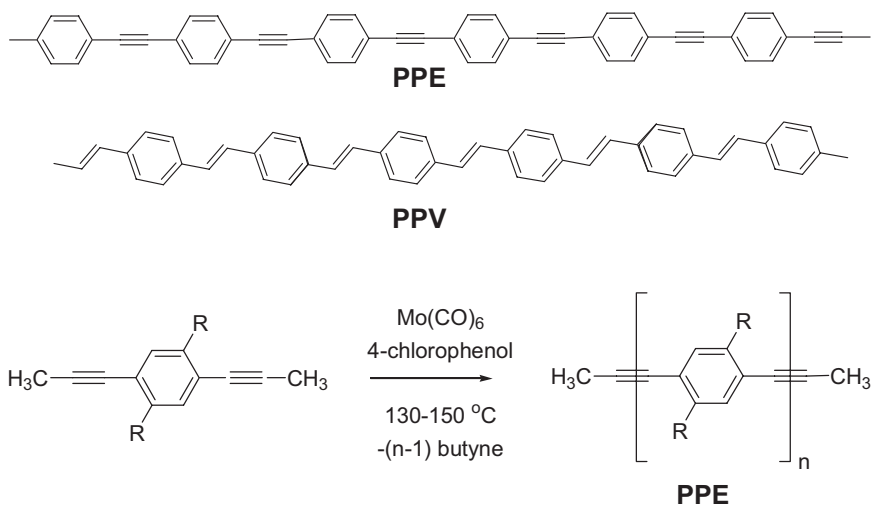
ADIMET chemistry was used on only rare occasions. On the other hand, the simple *in situ* catalysts described by Mortreux and Villemain and later used by Mori were sufficiently interesting to develop more active and selective tuned-up ADIMET catalysts [16, 18–20].

3.10.2.1

Synthesis of PPEs by *in situ* ADIMET

Conjugated polymers are organic semiconductors and as such are valuable as active layers in organic semiconductor devices that include, but are not restricted to, light-emitting diodes, thin film transistors, and photovoltaic cells [28–30]. The conjugated polymers that “made it big” were the PPVs shown by Friend [31] to be excellent emitters in polymeric light-emitting diodes and useful in other device types. Their dehydrogenated congeners, the PPEs, had been much less examined with respect to their physical properties and their device applications, despite their superior photophysics in comparison to that of the PPVs, at least in solution [5]. There should be significant opportunities in this field; even fundamental physical properties such as liquid crystallinity, thermochromism, solvatochromism, etc., of PPEs were not known until recently, even though PPEs had been reported as early as 1990 [32].

Mixtures of $\text{Mo}(\text{CO})_6$ and 4-chlorophenol are active in the polymerization of dipropynylated dialkylbenzenes to furnish dialkyl-PPEs of high molecular weight in quantitative yields (Scheme 3.10-11) [33]. Increasing the temperature from 105 °C (Mori) to 130–150 °C and removing the metathesis byproduct butyne by a gentle stream of dry nitrogen does the trick. While this protocol works well for



Scheme 3.10-11. Effective ADIMET with catalyst systems formed from $\text{Mo}(\text{CO})_6$ and 4-chlorophenol or 4-trifluoromethylphenol in *ortho*-dichlorobenzene [33].

Tab. 3.10-1. Substituent pattern and molecular weights for representative PPEs.

Substituent	Hexyl	Hexyl	Hexyl	2-Ethylbutyl	2-Ethylhexyl	Dodecyl
Temp (°C)	120	170	150	150	150	150
Co-catalyst	4-Cl-phenol	4-Cl-phenol	4-CF ₃ -phenol	4-CF ₃ -phenol	4-CF ₃ -phenol	4-Cl-phenol
Yield (%)	70	76	99	80	99	96
P _n (GPC)	22	10	94	Insoluble	510	770

dialkyl-PPEs, it mostly failed for dialkoxy-substituted PPEs. Table 3.10-1 shows that the optimum temperature for the ADIMET polymerization is 150 °C; at lower or higher temperatures, yields and P_n decrease. Dihexyl-PPE formed almost quantitatively under the optimized conditions, but its P_n was only around 100. However, this PPE was almost insoluble, and the moderate P_n therefore could have been an effect of the insufficient solubilizing power of the hexyl groups or lack of catalyst efficiency. Changing the solubilizing groups from hexyl to either the branched 2-ethylhexyl or the dodecyl groups increased the molecular weights of the obtained PPEs. According to gel permeation chromatography (GPC), these polymers have P_n values of up to 800 repeating units (Table 3.10-1) [34]. GPC overestimates the molecular weights of rigid rods, but only by a factor ranging from 1.3–1.8, so that P_n of metathesis-made PPEs is substantial, even if corrected for the error in the GPC measurements. They easily surpass the P_n of 50–100 typically obtained for PPEs made by the Pd route. The ADIMET reaction can be scaled up, and up to 20 g of PPE can be made in a 500-ml flask; the PPEs are isolated after aqueous workup and precipitation as yellow solids. In Figure 3.10-1 a sample of 20 g of PPE is shown.

To demonstrate that the high-molecular-weight PPEs are defect free, a ¹³C NMR spectrum of dinonyl-PPE is presented in Figure 3.10-2. The signal at $\delta = 93$ ppm is

**Fig. 3.10-1.** Sample of 20 g of didodecyl-PPE.

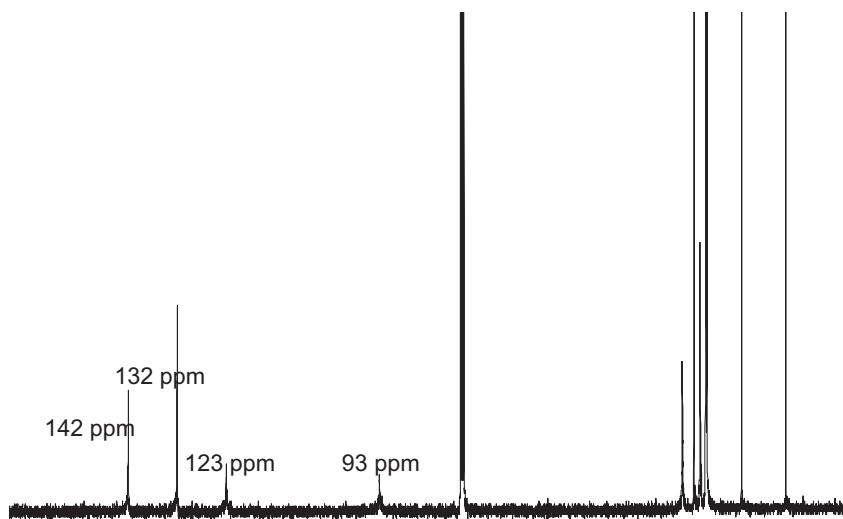
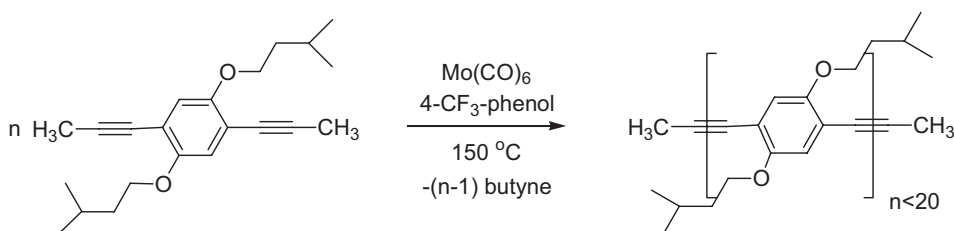


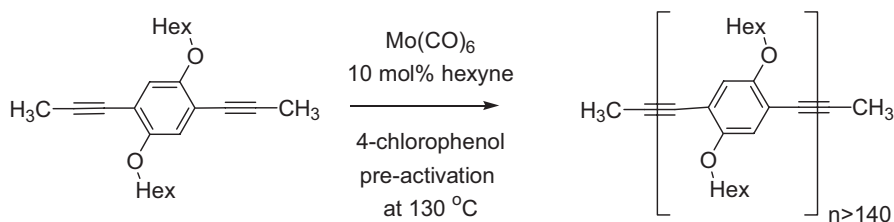
Fig. 3.10-2. ^{13}C NMR spectrum of dinonyl-PPE in CDCl_3 . The intensity of the alkyl signals is cut off for clarity.



Scheme 3.10-12. Ineffective synthesis of dialkoxy-PPEs by *in situ* ADIMET.

assigned to the alkyne carbons in the PPE, while the three signals at $\delta = 123$, 132 , and 142 are due to the resonances of the benzene ring. No additional peaks are visible in the aromatic or the vinylic region. Neither cross-linking nor formation of arenes in a molybdenum-mediated $[2+2+2]$ cycloaddition seems to interfere significantly with the alkyne metathesis process.

At the outset it was of interest if dialkoxy-PPEs could be made utilizing the *in situ* catalysts (Scheme 3.10-12). It was curious to notice that if an isopentyloxy-substituted monomer was used, a mixture of $\text{Mo}(\text{CO})_6$ and 4-trifluoromethylphenol was sufficiently active to give a short polymer (Scheme 3.10-12). Attempts to use other solubilizing alkoxy side chains failed, and the catalyst mixture was insufficient to perform alkyne metathesis. With the development of the “super” *in situ* catalysts (*vide supra*) [23], di(hexoxy)dipropynylbenzene metathesized to give the corresponding polymer (Scheme 3.10-13) in high yields and with a substantial $P_n > 140$. The “pre-activated” catalysts obviate 4-trifluoromethylphenol as co-catalyst, and the cheap 4-chlorophenol can be used without any problems.

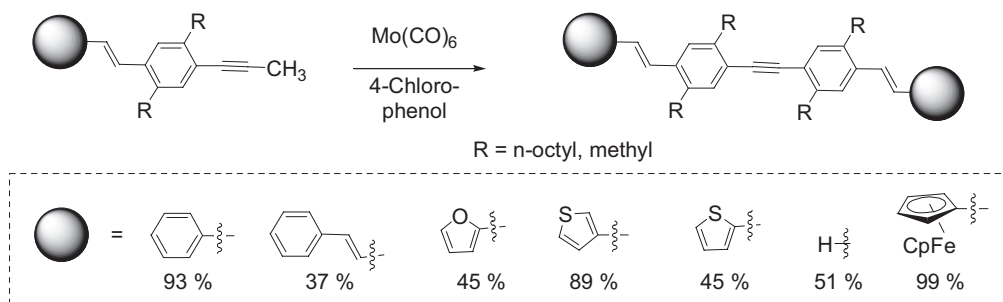


Scheme 3.10-13. Effective synthesis of dialkoxy-PPEs by “super” *in situ* ADIMET [23].

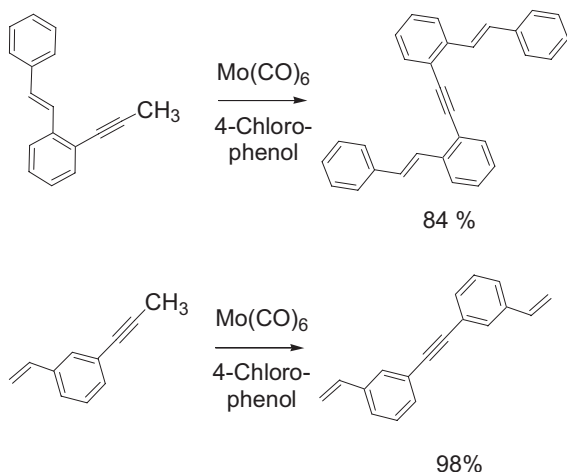
3.10.2.2

Synthesis of PPE-PPV Copolymers by *in situ* ADIMET

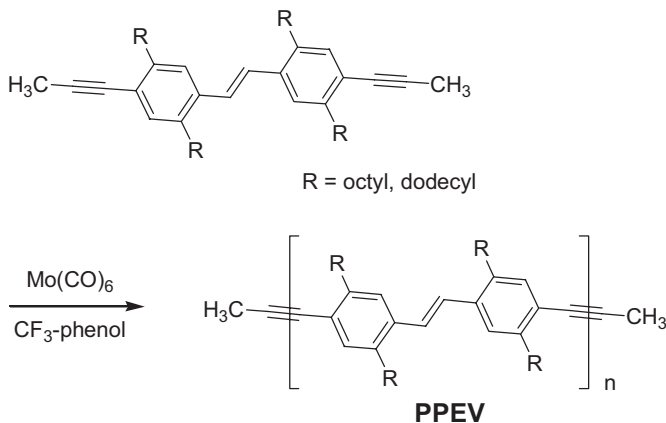
The usefulness of ADIMET with simple catalyst systems would be restricted if only PPEs could be made. It was exciting to explore which functionalities would tolerate the relatively harsh metathesis conditions utilizing hot 4-chlorophenol; it was fundamentally important to check whether C–C double bonds would survive ADIMET with *in situ* catalysts. Schrock reported that stoichiometric alkyne metathesis with carbyne complexes proceeds for vinyl-substituted internal alkynes, but these reaction conditions are much milder than the ones employed for the *in situ* catalysts [36]. Schemes 3.10-14 and 3.10-15 show that substrates that carry alkene groups are smoothly metathesized by the *in situ* catalysts. The isolated yields of the metathesis products range from 37% if butadiene groups are present to 99% for an organometallic stilbene-type substrate [35]. Even propynylated styrenes undergo the dimerization reaction smoothly with the *in situ* catalysts; hot 4-chlorophenol is apparently not sufficiently electrophilic to cause any problems. (Schemes 3.10-14 and 3.10-15). With these preliminary studies it was anticipated that the synthesis of PPE-PPV copolymers (PPEV) should be feasible (Scheme 3.10-16). The good compatibility of the *in situ* catalyst systems with double bonds was gratifying, because (1) systems similar to the ones employed here have been used by Wagener [11b] and Weder [11a] to perform olefin metathesis and (2) alkyne metathesis of enynes leads to the incorporation of the alkyne into the final product. Grubbs and Zuercher have cleverly utilized this scheme to make a series of polycyclic hydro-



Scheme 3.10-14. Alkenes in alkyne metathesis I.



Scheme 3.10-15. Alkenes in alkyne metathesis II.



Scheme 3.10-16. ADIMET synthesis of the PPE-PPV hybrid polymers [35, 39].

carbons [37]. An interesting aspect of the chemistry shown in Scheme 3.10-14 is that of the thiophene-containing substrates. While the propynyls shown here work fine, propynyl- and dipropynylthiophene [38a] and their derivatives metathesize neither with Schrock carbyne complexes nor with the Fürstner catalysts; only cross-metathesis is feasible if a molybdenum-based catalyst is used [38b]. It seems that the thiophene sulfur interacts with the catalysts by chelation, but if the spatial separation between sulfur and metal is sufficient, thiophene units are tolerated by all available catalyst systems.

Dipropynylated stilbenes (see Scheme 3.10-16) undergo ADIMET if the more active trifluoromethylphenol is used in the presence of Mo(CO)_6 . As in the other cases, temperatures between 130 °C and 150 °C are necessary. A series of PPEVs formed in high yields with P_n values ranging from 40 to 150. The PPEVs were

isolated by precipitation of the reaction mixture into methanol. They are stable, fluorescent greenish-yellow, almost amorphous solids and are currently being investigated for use in organic light-emitting diodes [39]. In the evolution of this concept, larger monomers furnish the more complex alkyne-bridged polymers shown in Scheme 3.10-17.

Organometallic and anthracene-containing monomers can be metathesized to give PAEs with novel structures and potentially interesting redox properties [40]. ADIMET gives such polymers in high yields with P_n values ranging from 40 to 80. Due to the relatively complex synthesis of the monomers, these are made on a 200–500 mg scale; purification is less effective on this scale than for monomers that are available on a 2–25 g scale. The lower molecular weights of these polymers can be attributed to the less satisfactory purity of the utilized monomers.

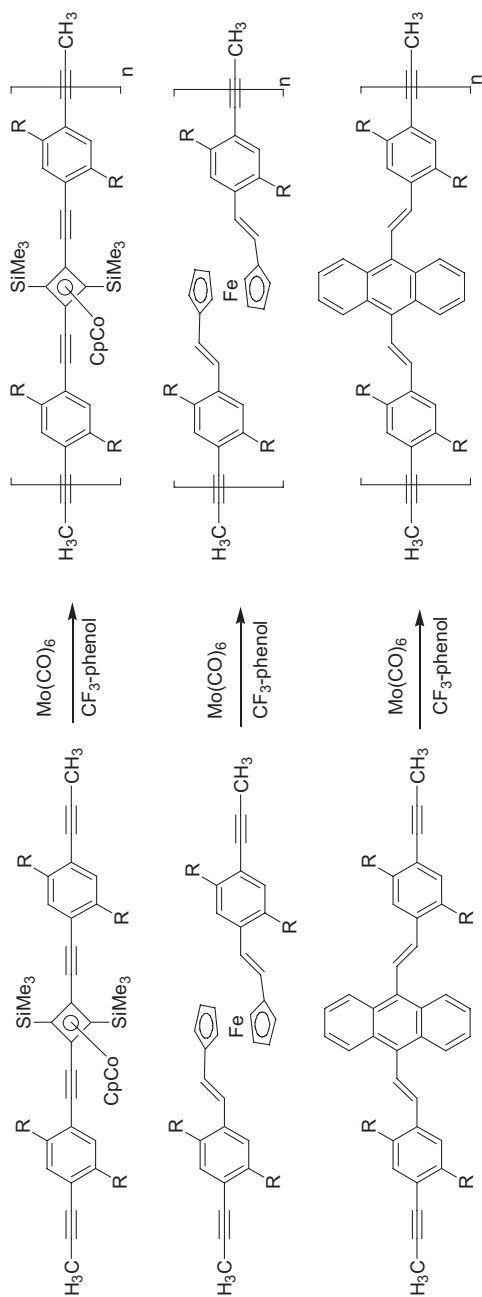
3.10.2.3

Synthesis of Other PAEs by ADIMET

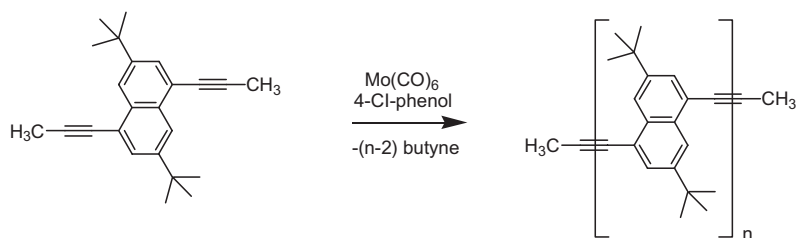
ADIMET should be feasible with any dipropynylated aromatic compound to give high-quality PAEs with novel structures and properties: iodination of 3,7-*di*-*tert*-butylnaphthalene, followed by propynylation, gives 1,5-dipropynyl-3,7-*di*-*tert*-butylnaphthalene. ADIMET of this monomer furnishes PNE (Scheme 3.10-18) in high yield as a brittle, tan-colored material that is quite insoluble in common organic solvents and non-fluorescent in the solid state. As such, *di*-*tert*-butyl-substituted PNE is not very useful [42].

To improve the properties of the PNE, a series of copolymers containing naphthalene and benzene rings was made by co-ADIMET of two monomers (Scheme 3.10-19) [43]. These polymers (PPNE) formed smoothly and in good to excellent yields as film-forming, soluble materials with a P_n of 40–100 repeating units. The PPNEs showed nematic liquid crystalline behavior, strong blue emission in the solid state (see Figure 3.10-3), and promising electroluminescent characteristics [44].

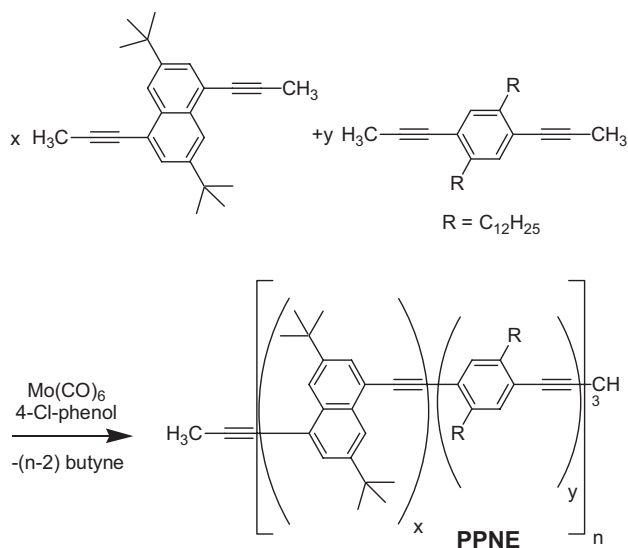
At the same time, other aromatics were explored as modules for (polyarylene-ethynylene)s. Polyfluorenes (PF) are a class of important conjugated polymers [3] that are utilized in blue light-emitting diodes. PF's emission maximum is at 380 nm, in the ultraviolet, and not at 430 nm, where it would match the human eye's sensitivity for blue. Dialkyl-PF's high stability and processibility make it an industrially interesting emitter material. At the same time, there are fascinating questions of fundamental importance with regard to PF's optical and emissive behavior in solution, in the solid state, and in working devices: PF-based LEDs experience a bathochromic shift in emission (a shoulder grows in at 510 nm) upon prolonged operation that changes the device color from blue to green. The occurrence of this red-shifted feature detected by Scherf [3] was mostly attributed to excimer emission, even though its genesis was not clear. At the time when Scherf's article appeared, we were interested in making a fluorene-based material that would be peak emissive in the blue at 420–430 nm, where the sensitivity of the eye is matched. We reasoned that the introduction of alkyne groups between the



Scheme 3.10-17. ADIMET synthesis of novel polyaryleneethynylene copolymers [40, 41].



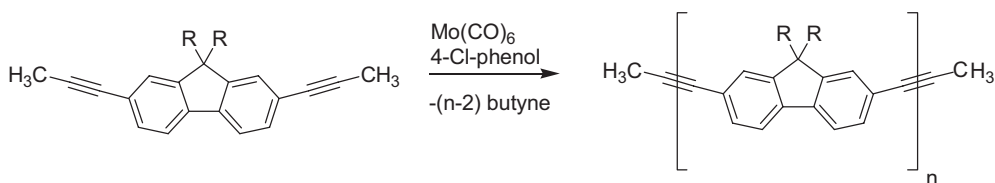
Scheme 3.10-18. Synthesis of poly[1,5-(3,7-di-*tert*-butyl)naphthyleneethynylene] (PNE) by ADIMET [42].



Scheme 3.10-19. Synthesis of PNE-PPE copolymers by ADIMET [43].



Fig. 3.10-3. Solid-state emission of a series of PPNEs. From left to right: pure PPE, 33% naphthalene, 50% naphthalene, 75% naphthalene, pure PNE.



Scheme 3.10-20. Synthesis of poly(fluorenyleneethynylene)s (PFE) by ADIMET [45].

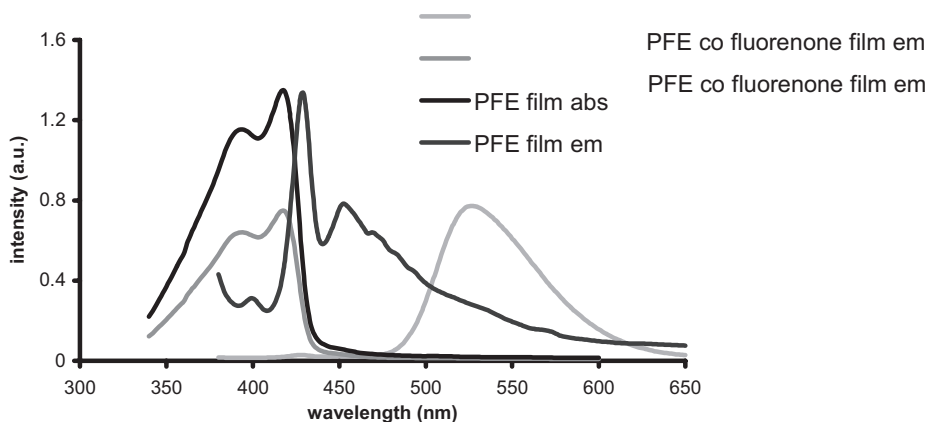
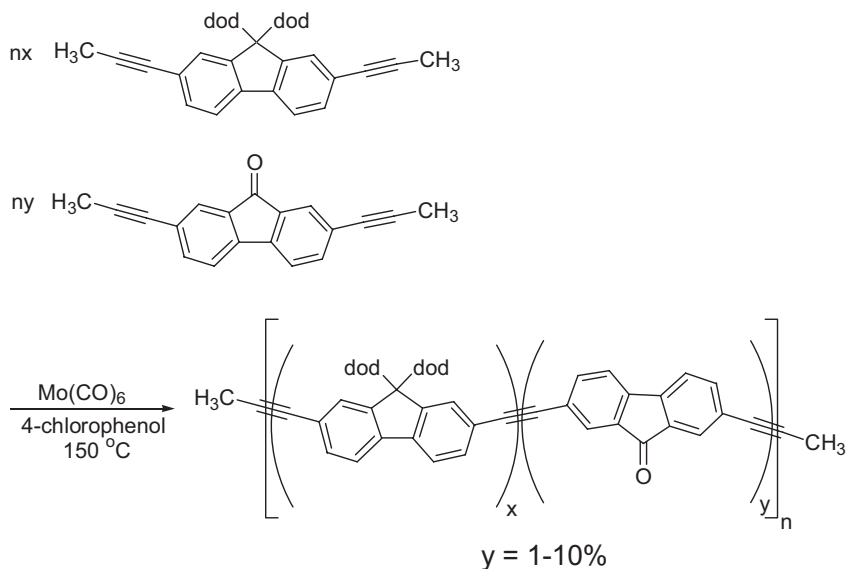


Fig. 3.10-4. Solution and solid-state absorption and emission of PFE and fluorenone-doped PFE absorption and emission in thin solid films [46].

fluorene nuclei would lead to a bathochromic shift in emission. ADIMET of di(dodecyl)propynylfluorene furnished poly[(didodecyl)fluorenyleneethynylene)s (PFE) of high molecular weight in excellent yields (Scheme 3.10-20) [44]. Figure 3.10-4 shows that the emission of the PFEs in thin films peaks at 430 nm, i.e., the material is a solid-state blue emitter. The solution phase and the solid-state emission spectra of the PFEs are almost superimposable; excimer formation does not seem to play a big role in these materials, and in an ongoing cooperation with Dupont, we were able to fabricate promising blue and white proof of concept LEDs [46].

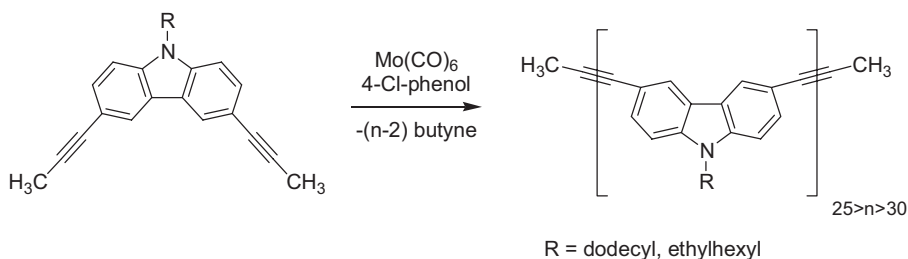
Doping of conjugated polymers usually means either reduction or oxidation under direct electrical or oxidative/reductive charging. In most cases doped conjugated polymers are non-fluorescent but conducting [47]. Doping in inorganic semiconductor chemistry and electrical engineering, on the other hand, means the introduction of a dopant that has a different band structure (HOMO-LUMO gap) than the bulk material. The dopant's band levels will determine the semiconducting and electronic properties of the formed compound semiconductor [48]. In organic polymers, this doping concept should be applicable if two monomers with markedly different electronic properties are copolymerized [49]. We decided to test this assumption for the specific case of the PFEs. Di(dodecylpropynyl)-fluorene was co-metathesized with 1–10 mol% of di(propynyl)fluorenone



Scheme 3.10-21. Synthesis of fluorenone-doped poly(fluorenyleneethynylene) polymers by ADIMET [46].

(Scheme 3.10-21). Fortuitously, di(propynyl)fluorenone was smoothly incorporated into the PFE and did not decrease the activity of the *in situ* catalyst system; this is an interesting finding because Schrock-type molybdenum and tungsten-carbene complexes react with ketones and aldehydes under a Wittig-analogous olefination. The *in situ* ADIMET catalysts, however, coped well with the presence of the keto groups, and the fluorenone-doped PFEs were obtained in high yield and with a P_n of approximately 40 repeating units (Scheme 3.10-21).

In solution, PFEs and fluorenone-doped PFEs show identical absorption and emission spectra; however, in thin films, the emission of the doped PFE is dramatically red-shifted to 520 nm. Such films are highly orange emissive, and none of the blue emission remains in the solid state (Figure 3.10-4). The fluorenone modules function as solid-state defects and energy traps, dopants, that lead to the emission at 520 nm. The red shift is due to the fluorenone's decreased LUMO. Interestingly, the change in the emission is visible only in the solid state, suggesting some form of three-dimensional through-space conjugation in doped PFEs. This emission behavior of doped PFEs looks similar to that what in PF-based light-emitting diodes had been attributed to excimer formation [3]. Keto defects in the backbone and not excimer formation could lead to the bathochromically shifted emission in the PFs; very recently Scherf actually found direct evidence for this phenomenon in working PF devices [3b]. He concluded that photooxidation during device operation cleaves the alkyl groups off the fluorene nucleus and that fluorenone defects are formed in the PFs. Doping with the fluorenone units changes PF's emission with an effect very similar to that observed by us for the solid-state emission of fluorenone-doped PFEs [49b].



Scheme 3.10-22. Synthesis of alkyne-bridged carbazole polymers (PCE) by ADIMET [51].

3.10.2.4

Alkyne-Bridged Carbazole Polymers (PCE) by ADIMET [50]

Heteroatoms are well tolerated in the ADIMET process by the *in situ* catalysts if they are far enough removed from the site of reaction, and chelation of the catalyst is not possible. We prepared a series of *N*-alkyl-dipropynylcarbazoles and performed their ADIMET reaction to isolate carbazole-containing poly(arylene-ethynylene)s (PCE) in high yields and P_n values at around 30 (Scheme 3.10-22) [51]. The film-forming polymers are beige-colored, almost non-fluorescent powders, that are soluble in common organic solvents. The reason for the somewhat disappointing emissive properties of these materials is the break of conjugation by the double *meta* orientation of the alkyne groups with respect to each other. This topology shuts down the electronic interactions between the carbazole groups and makes PCEs practically non-conjugated. When copolymerized with dialkylidene(propynyl)benzenes, random copolymers with an interesting pH-dependant emission result that are under investigation as solid-state proton sensors [51].

3.10.3

Conclusions

Acyclic diyne metathesis has made great strides in the last five years and has evolved from an interesting chemical “glass bead game” into a powerful synthetic methodology to make conjugated polymers and natural [14] and unnatural products [52]. At the moment, two different approaches are pursued. One can work with defined catalysts of the Schrock, Fürstner, or Cummins type. These are active, but the preparation of the (commercially non-available) catalysts is costly in terms of involved labor, expertise, and equipment. On the other hand, one can use the *in situ* catalysts formed from $\text{Mo}(\text{CO})_6$ and acidic phenols in a protocol similar to that developed by Villemain in the early 1980s [16, 18–22]. While the *in situ* catalysts were *a priori* not as active as the defined molybdenum or tungsten carbynes, careful optimization has considerably increased their activity. New hexyne-pre-activated mixtures of $\text{Mo}(\text{CO})_6$ and 4-chlorophenol allow the effective metathesis of the otherwise problematic enyne substrates and monomers carrying chelating oxygen

functionalities [23]. The current *in situ* catalyst metathesizes almost all substrates, even though the necessary reaction temperatures are 30–60 °C higher than if the defined molybdenum- or tungsten-carbyne complexes are utilized. In the investigated examples, thermal sensitivity of the substrates or products has not been a problem, and the stability of the employed monomers is generally more than sufficient to allow for their successful metathesis. *In situ* catalysts are robust and efficient, withstand high temperatures, and form from commercially available, inexpensive starting materials in technical solvents in a trivial experimental setup. Interesting and pressing questions remain: What is the actual nature of the involved catalyst? Can water and other protic solvents be utilized as working media for *in situ* catalysts? Can ADIMET be performed in supercritical CO₂? And last but not least, will it be possible to demetathesize conjugated alkyne-bridged polymers into their monomers in the presence of any internal alkyne by this elegant synthetic method? We have just started to scratch the surface in this fascinating field of research.

Acknowledgments

I thank my talented coworkers Dr. Lioba Kloppenburg, Dr. Neil G. Pschirer, Dr. Winfried Steffen, Dr. Ping-Hua Ge, Dr. Glen Brizius, Dschun Song, Alan Marshall, Steve Kroth, and David Jones for their untiring efforts in the area of alkyne metathesis, and the National Science Foundation (NSF CHE 9814-118 (1999–2001) and CHE 0138-659 (2002–2004)), the Petroleum Research Funds, the Research Corporation, The Henry and Camille Dreyfus Foundation, and the University of South Carolina and the South Carolina NANOCENTER for generous funding.

References

- 1 BRINTZINGER, H. H.; FISCHER, D.; MÜHLHAUPT, R.; RIEGER, B.; WAYMOUTH, R. M. *Angew. Chem.* **1995**, *34*, 1143. MCKNIGHT, A. L.; WAYMOUTH, R. M. *Chem. Rev.* **1998**, *98*, 2587. ITTEL, S. D.; JOHNSON, L. K.; BROOKHART, M. *Chem. Rev.* **2000**, *100*, 1167. COATES, G. W. *Chem. Rev.* **2000**, *100*, 1223. BOFFA, L. S.; NOVAK, B. M. *Chem. Rev.* **2000**, *100*, 1479.
- 2 REHAHN, M.; SCHLÜTER, A. D.; WEGNER, G. *Macromol. Chem.* **1990**, *191*, 1991. REHAHN, M.; SCHLÜTER, A. D.; WEGNER, G.; FEAST, W. J. *Polymer* **1990**, *30*, 1060. SCHLÜTER, A. D.; WEGNER, G. *Acta Polym.* **1993**, *44*, 59.
- 3 (a) SCHERF, U.; LIST, E. J. W. *Adv. Mater.* **2002**, *14*, 447. (b) LIST, E. J. W.; GUENTNER, R.; SCANDUCCI DE FREITAS, P.; SCHERF, U. *Adv. Mater.* **2002**, *14*, 374. (c) NEHER, D. *Macromol. Rapid Commun.* **2001**, *22*, 1366. (d) BERNIUS, M. T.; INBASEKARAN, M.; O'BRIEN, J.; WU, W. S. *Adv. Mater.* **2000**, *12*, 1737.
- 4 (a) CONTICELLO, V. P.; GIN, D. L.; GRUBBS R. H. *J. Am. Chem. Soc.* **1992**, *114*, 9708. SCHERF, U. *Top. Curr. Chem.* **1999**, *201*, 163. WAGAMAN, M. W.; GRUBBS, R. H. *Macromolecules* **1997**, *30*, 3978. (b) BAZAN, G. C.; MIAO, Y. J.; RENAK, M. L.; SUN, B. J. *J. Am. Chem. Soc.* **1996**, *119*, 2618. (c) For general alkene metathesis see: TRNKA, T. M.; GRUBBS, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. GRUBBS, R. H.; CHANG, S. *Tetrahedron* **1998**, *54*, 4413. GRUBBS, R. H.; MILLER, S. J.; FU, G. C. *Acc. Chem. Res.* **1995**, *28*,

446. b) for polyacetylene see MOORE, J. S.; GORMAN, C. B.; GRUBBS, R. H. *J. Am. Chem. Soc.* **1991**, *113*, 1704.
- 5 (a) BUNZ, U. H. F. *Chem. Rev.* **2000**, *100*, 1605. HALKYARD, C. E.; RAMPEY, M. E.; KLOPPENBURG, L.; STUDER-MARTINEZ, S. L.; BUNZ, U. H. F. *Macromolecules* **1998**, *31*, 8655. (b) MANGEL, T.; EBERHARDT, A.; SCHERF, U.; BUNZ, U. H. F.; MÜLLEN, K. *Macromol. Rapid Commun.* **1995**, *16*, 571. (c) ZHOU, Q.; SWAGER, T. M. *J. Am. Chem. Soc.* **1995**, *117*, 12593. JANG, J. S.; SWAGER, T. M. *J. Am. Chem. Soc.* **1998**, *120*, 11864. KIM, J.; SWAGER, T. M. *Nature* **2001**, *411*, 1030.
- 6 REDDINGER, J. L.; REYNOLDS, J. R. *Adv. Polym. Sci.* **1999**, *145*, 57. RONCALI, J. *Chem. Rev.* **1992**, *92*, 711. CHEN, T. A.; WU, X. M.; RIEKE, R. D. *J. Am. Chem. Soc.* **1995**, *117*, 233.
- 7 POLITIS, J. K.; NEMES, J. C.; CURTIS, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 2537.
- 8 POLITIS, J. K.; CURTIS, M. D.; HE, Y.; KANICKI, J. *Macromolecules* **1999**, *32*, 2484.
- 9 NITSCHKE, J. R.; TILLEY, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 5365. MAO, S. S. H.; TILLEY, T. D. *J. Am. Chem. Soc.* **1995**, *117*, 5365.
- 10 (a) MASUDA, T. see chapter about alkyne polymerization with classic catalysts in this volume. (b) For an exception to the rule of internal alkyne see: MORTREUX, A.; PETTIT, F.; PETTIT, M.; SZYMANSKA-BUZAR, T. *J. Mol. Catal. A* **1995**, *96*, 95.
- 11 (a) STEIGER, D.; WEDER, C.; SMITH, P. *Macromolecules* **1999**, *32*, 5391. (b) GOMEZ, F. J.; WAGENER, K. B. *Macromol. Chem. Phys.* **1998**, *199*, 1581. GOMEZ, F. J.; MANAK, M. S.; ABBOUD, K. A.; WAGENER, K. B. *J. Mol. Catal. A* **2000**, *160*, 145.
- 12 IVIN, K. J.; MOL, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego **1997**, 2nd Edition.
- 13 SCHROCK, R. R. *J. Chem. Soc. Dalton* **2001**, 2541. FELDMAN, J.; SCHROCK, R. R. *Prog. Inorg. Chem.* **1991**, *39*, 1. SCHROCK, R. R. *Chem. Rev.* **2002**, *102*, 145. SCHROCK, R. R. *Acc. Chem. Res.* **1990**, *23*, 158. For the synthesis of the popular $(t\text{BuO})_3\text{W}=\text{C}(\text{tBu})$: SCHROCK, R. R.; CLARK, D. N.; SANCHEZ, J.; WENGROVIUS, J. H.; ROCKLAGE, S. M.; PEDERSEN, S. F. *Organometallics* **1982**, *1*, 1645. LISTEMANN, M. L.; SCHROCK, R. R. *Organometallics* **1985**, *4*, 74.
- 14 (a) FÜRSTNER, A.; GUTH, O.; RUMBO, A.; SEIDEL, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. FÜRSTNER, A.; MATHES, C.; LEHMANN, C. W. *Chemistry, Eur. J.* **2001**, *7*, 5299. FÜRSTNER, A.; SEIDEL, G. *Angew. Chem.* **1998**, *37*, 1734. (b) see FÜRSTNER, A. alkyne metathesis, chapter in this volume.
- 15 TSAI, Y. C.; DIACONESCU, P. L.; CUMMINS, C. C. *Organometallics* **2000**, *19*, 5260.
- 16 KANETA, N.; HIKICHI, K.; ASAKA, S.; UEMURA, M.; MORI, M. *Chem. Lett.* **1995**, 1055. KANETA, N.; HIRAI, T.; MORI, M. *Chem. Lett.* **1995**, 627.
- 17 FRITCH, J. R.; VOLLHARDT, K. P. C. *Angew. Chem.* **1979**, *18*, 409.
- 18 BUNZ, U. H. F.; KLOPPENBURG, L. *Angew. Chem.* **1999**, *38*, 478. MORTREUX, A.; BLANCHARD, M. *Chem. Commun.* **1974**, 786. BRAY, A.; MORTREUX, A.; PETIT, F.; PETIT, M.; SZYMANSKA-BUZAR, T. *Chem. Commun.* **1993**, 197.
- 19 VILLEMIN, D.; CADIOT, P. *Tetrahedron Lett.* **1982**, *23*, 5139.
- 20 VILLEMIN, D.; HEROUX, M.; BLOT, V. *Tetrahedron Lett.* **2001**, *42*, 3701.
- 21 (a) NISHIDA, M.; SHIGA, H.; MORI, M. *J. Org. Chem.* **1998**, *63*, 8606. (b) For metal mediated [2+2+2]cycloaddition see VOLLHARDT, K. P. C. *Angew. Chem.* **1984**, *23*, 539. VOLLHARDT, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1.
- 22 PSCHIRER, N. G.; BUNZ, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481.
- 23 BRIZIUS, G.; BUNZ, U. H. F. *Org. Lett.* **2002**, submitted.
- 24 KROUSE, S. A.; SCHROCK, R. R. *Macromolecules* **1989**, *22*, 2569. KROUSE, S. A.; SCHROCK, R. R.; COHEN, R. E. *Macromolecules* **1987**, *20*, 903.
- 25 ZHANG, X. P.; BAZAN, G. C. *Macromolecules* **1994**, *27*, 4627.
- 26 WEISS, K.; MICHEL, A.; AUTH, E. M.; BUNZ, U. H. F.; MANGEL, T.; MÜLLEN, K. *Angew. Chem.* **1997**, *36*, 506.

- 27 GOODSON, F. E.; WALLOW, T. I.; NOVAK, B. M. Mechanistic studies on the aryl-aryl interchange reaction of ArPdL_2I (L = triarylphosphine) complexes. *J. Am. Chem. Soc.* **1997**, *119*, 12441–12453.
- 28 KRAFT, A.; GRIMSDALE, A. C.; HOLMES, A. B. Electroluminescent conjugated polymers – Seeing polymers in a new light. *Angew. Chem.* **1998**, *37*, 402.
- MITSCHKE, U.; BÄUERLE, P. *J. Chem. Mater.* **2000**, *10*, 1471.
- 29 BAO, Z. N.; LOVINGER, A. J. *Chem. Mater.* **1999**, *11*, 2607. BAO, Z. N.; LOVINGER, A. J.; BROWN, J. J. *Am. Chem. Soc.* **1998**, *120*, 207.
- 30 BRABEE, C. J.; SARICITCI, N. S.; HUMMELEN, J. C. *Adv. Funct. Mater.* **2001**, *11*, 15. YU, G.; GAO, J.; HUMMELEN, J. C.; WUDL, F.; HEEGER, A. J. *Science* **1995**, *270*, 1789. HALLS, J. M.; WALSH, C. A.; GREENHAM, N. C.; MARSEGLIA, E. A.; FRIEND, R. H.; MORATTI, S. V.; HOLMES, A. B. *Nature* **1995**, *376*, 498.
- 31 BURROUGHS, J. H.; BRADLEY, D. D. C.; BROWN, A. R.; MARKS, R. N.; MACKAY, K.; FRIEND, R. H.; BURNS, P. L.; HOLMES, A. B. *Nature* **1990**, *347*, 539.
- 32 GIESA, R.; SCHULZ, R. C. *Macromol. Chem. Phys.* **1990**, *191*, 857. a) WEDER C.; WRIGHTON, M. S. *Macromolecules* **1996**, *29*, 5157. WRIGHTON, M. S.; OFER, D.; SWAGER, T. M. *Chem. Mater.* **1995**, *7*, 418. SWAGER, T. M.; GIL, C. J.; WRIGHTON, M. S. *J. Phys. Chem.* **1995**, *99*, 4886. LI, H.; POWELL, D. R.; HAYASHI, R. K.; WEST, R. *Macromolecules* **1998**, *31*, 52–58.
- 33 BUNZ, U. H. F. *Acc. Chem. Res.* **2001**, *34*, 998.
- 34 KLOPPENBURG, L.; SONG, D.; BUNZ, U. H. F. *J. Am. Chem. Soc.* **1997**, *120*, 7973. KLOPPENBURG, L.; JONES, D.; BUNZ, U. H. F. *Macromolecules* **1999**, *32*, 4194.
- 35 BRIZIUS, G.; PSCHIRER, N. G.; STEFFEN, W.; STITZER, K.; ZUR LOYE, H.-C.; BUNZ, U. H. F. *J. Am. Chem. Soc.* **2000**, *122*, 12435.
- 36 LISTEMANN, M. L.; SCHROCK, R. R. *Organometallics* **1985**, *4*, 74.
- 37 ZUERCHER, W. J.; SCHOLL, M.; GRUBBS, R. H. *J. Org. Chem.* **1998**, *63*, 4291. KIM, S. H.; ZUERCHER, W. J.; BOWDEN, N. B.; GRUBBS, R. H. *J. Org. Chem.* **1996**, *61*, 1073.
- 38 FÜRSTNER, A.; MATHES, C. *Org. Lett.* **2001**, *3*, 221.
- 39 EGBE, D. A. M.; TILLMANN, H.; BIRCKNER, E.; KLEMM, E. *Macromol. Chem. Phys.* **2001**, *202*, 2712. PAUTZSCH, T.; KLEMM, E. *Macromolecules* **2002**, *35*, 1569. EGBE, D. A. M.; ROLL, C. P.; BIRCKNER, E.; GRUMMT, U. W.; STOCKMANN, R.; KLEMM, E. *Macromolecules* **2002**, *35*, 3825.
- 40 STEFFEN, W.; KÖHLER, B.; ALTMANN, M.; SCHERF, U.; STITZER, K.; ZUR LOYE, H. C.; BUNZ, U. H. F. *Chemistry Eur. J.* **2001**, *7*, 117.
- 41 BUNZ, U. H. F.; BRIZIUS, G. *unpublished results*.
- 42 PSCHIRER, N. G.; MARSHALL, A. R.; STANLEY, C.; BECKHAM, H. W.; BUNZ, U. H. F. *Macromol. Rapid Commun.* **2000**, *21*, 493.
- 43 PSCHIRER, N. G.; VAUGHN, M. E.; DONG, Y. B.; ZUR LOYE, H. C.; BUNZ, U. H. F. *Chem. Commun.* **2000**, 85.
- 44 PSCHIRER, N. G.; MITEVA, T.; EVANS, U.; ROBERTS, R. S.; MARSHALL, A. R.; NEHER, D.; MYRICK, M. L.; BUNZ, U. H. F. *Chem. Mater.* **2001**, *13*, 2691.
- 45 (a) PSCHIRER, N. G.; BUNZ, U. H. F. *Macromolecules* **2000**, *33*, 3961. (b) PSCHIRER, N. G.; BYRD, K.; BUNZ, U. H. F. *Macromolecules* **2001**, *34*, 8590.
- 46 UCKERT, F.; BUNZ, U. H. F.; PSCHIRER, N. G. *unpublished results*.
- 47 SHIRAKAWA, H. *Synthetic Met.* **2001**, *125*, 3. MACDIARMID, A. G. *Synthetic Met.* **2001**, *125*, 11. HEEGER, A. J. *Synthetic Met.* **2001**, *125*, 23. NAARMANN, H.; THEOPHILOU, N. *Synth. Met.* **1987**, *22*, 1. NAARMANN, H. *Synth. Met.* **1987**, *17*, 223. SCHERMAN, O. A.; GRUBBS, R. H. *Synthetic Met.* **2001**, *124*, 431.
- 48 BALL, P. *Made to Measure, New Materials for the 21st Century*, Princeton University Press, Princeton 1997.
- 49 (a) TASCH, S.; LIST, E. J. W.; HOCHFILZER, C.; LEISING, G.; SCHLICHTING, P.; ROHR, U.; GEERTS, Y.; SCHERF, U.; MÜLLEN, K. *Phys. Rev. B* **1997**, *56*, 4479. KLÄRNER, G.; LEE,

- J.-I.; DAVEY, M. H.; MILLER, R. D. *Adv. Mater.* **1999**, *11*, 115. LEE, J. I.; ZYUNG, T.; MILLER, R. D.; KIM, Y. H.; JEOUNG, S. C.; KIM, D. *J. Mater. Chem.* **2000**, *10*, 1547. (b) UCKERT, F.; SETAYESH, S.; MÜLLEN, K. *Macromolecules* **1999**, *32*, 4519. UCKERT, F.; TAK, Y. H.; MÜLLEN, K.; BÄSSLER, H. *Adv. Mater.* **2000**, *12*, 905.
- 50 TAO, X. T.; ZHANG, Y. D.; WADA, T.; SASABE, H.; SUZUKI, H.; WATANABE, T.; MIYATA, S. *Adv. Mater.* **1998**, *10*, 226. MORIN, J. F.; LECLERC, M. *Macromolecules* **2001**, *34*, 4680. SOTZING, G. A.; REDDINGER, J. L.; KATRITZKY, A. R.; SOLODUCHO, J.; MUSGRAVE, R.; REYNOLDS, J. R. *Chem. Mater.* **1997**, *9*, 1578.
- 51 BRIZIUS, G.; KROTH, S.; BUNZ, U. H. F. *Macromolecules* **2002**, *35*, accepted.
- 52 GE, P. H.; FU, W.; HERRMANN, W. A.; HERDTWECK, E.; CAMPANA, C.; ADAMS, R. D.; BUNZ, U. H. F. *Angew. Chem.* **2000**, *39*, 3607. PSCHIRER, N. G.; FU, W.; ADAMS, R. D.; BUNZ, U. H. F. *Chem. Commun.* **2000**, 87.

3.11

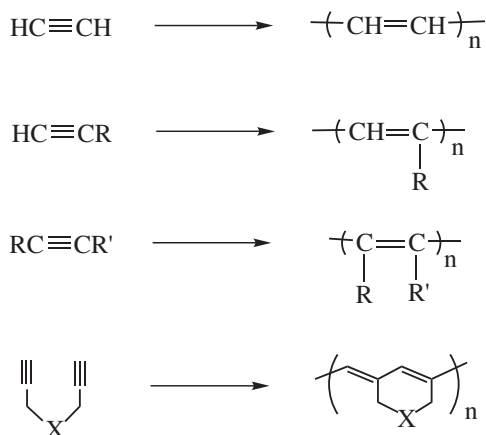
Polymerization of Substituted Acetylenes

Toshio Masuda and Fumio Sanda

3.11.1

Introduction

Acetylenes can be polymerized by chain growth in the presence of transition metal catalysts to give high-molecular-weight polymers (Scheme 3.11-1). The monomers include acetylene, mono- and disubstituted acetylenes, and α,ω -diynes. The polymers possess carbon-carbon alternating double bonds along the main chain and exhibit unique properties (e.g., metallic conductivity) that are not expected with vinyl polymers.



Scheme 3.11-1. Polymerization of acetylenes.

Polymerization of acetylene was first achieved by Natta and his coworkers using a Ti-based catalyst [1]. This polymerization, like the polymerization of olefins, proceeds by the insertion mechanism. Because of the lack of processability and stability, early studies on polyacetylenes were motivated by only theoretical and spectroscopic interests. Then the discovery of the metallic conductivity of doped

polyacetylene [2] stimulated research into the chemistry of polyacetylene, and now polyacetylene is recognized as one of the most important conjugated polymers. From the viewpoint of synthesis of polyacetylene, two breakthroughs can be cited; one is the direct synthesis of polyacetylene membrane by using the Shirakawa catalyst, $\text{Ti}(\text{O}-n\text{-Bu})_4\text{-Et}_3\text{Al}$ at high concentration [3, 4], and the other is a modification of the aging method of the Shirakawa catalyst, which gives polyacetylene with fewer defects [5]. Many publications are available about the chemistry and physics of polyacetylene itself [6–9].

Introduction of side groups onto polyacetylene has been investigated to improve its processability and to endow it with unique properties and functions. Early attempts led to the conclusion that only sterically unhindered monosubstituted acetylenes can be polymerized with the Ziegler-type catalysts. Traditional ionic and radical initiators also turned out to lack the ability to provide high-molecular-weight polymers from substituted acetylenes. In 1974 the first successful polymerization of substituted acetylene was achieved when it was found that group 6 transition metals are quite active for the polymerization of phenylacetylene to provide a polymer with molecular weight over 10^4 [10]. After this finding, there has been much effort to develop highly active catalysts, to tune the polymer properties, and to precisely control the polymer structure. These energetic studies have produced a wide variety of polymers from acetylene derivatives, including mono- and disubstituted acetylenes and α,ω -diynes (Table 3.11-1). The carbon-carbon alternating double bonds in the main chain of these polymers provide an opportunity to obtain unique properties such as conductivity, nonlinear optical properties, magnetic properties, gas permeability, photo- and electroluminescent properties, etc., which are not accessible from the corresponding vinyl polymers.

Tab. 3.11-1. Acetylenes that form high-molecular-weight polymers.

	<i>Unsubstituted</i>	<i>Monosubstituted</i>	<i>Disubstituted</i>	<i>α,ω-Diyne</i>
Hydrocarbon	$\text{HC}\equiv\text{CH}$	$\text{HC}\equiv\text{C}-n\text{-Bu}$	$\text{MeC}\equiv\text{C}-n\text{-C}_5\text{H}_{11}$	
		$\text{HC}\equiv\text{C}-t\text{-Bu}$	$\text{MeC}\equiv\text{C}-\text{C}_6\text{H}_5$	
		$\text{HC}\equiv\text{C}-\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5-\text{C}\equiv\text{C}-\text{C}_6\text{H}_5-t\text{-Bu}$	
Heteroatom-containing		$\text{HC}\equiv\text{CCO}_2-n\text{-Bu}$	$\text{ClC}\equiv\text{C}-n\text{-C}_6\text{H}_{13}$	
		$\text{Me}_3\text{Si}-\text{C}_6\text{H}_4-\text{HC}\equiv\text{C}-\text{C}_6\text{H}_5$	$\text{ClC}\equiv\text{C}-\text{C}_6\text{H}_5$	
		$\text{CF}_3-\text{C}_6\text{H}_4-\text{HC}\equiv\text{C}-\text{C}_6\text{H}_5$	$\text{MeC}\equiv\text{CSiMe}_3$ $\text{C}_6\text{H}_5-\text{C}\equiv\text{C}-\text{C}_6\text{H}_5-\text{SiMe}_3$	

Tab. 3.11-2. Typical catalysts for the polymerization of acetylenes and reaction mechanism.^a

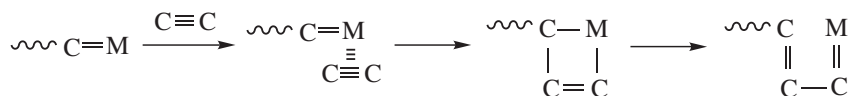
Group	4	5	6	8–10
Catalyst (Monomer ^a)	Ti(O- <i>n</i> -Bu) ₄ -Et ₃ Al (HC≡CH)	NbCl ₅ , TaCl ₅ (RC≡CR') TaCl ₅ - <i>n</i> -Bu ₄ Sn (PhC≡CC ₆ H ₄ - <i>p</i> -X)	MoCl ₅ - <i>n</i> -Bu ₄ Sn, WCl ₆ -Ph ₄ Sn (HC≡CR, RC≡CR') M(CO) ₆ -CCl ₄ -hν (M = Mo, W) (HC≡CR, ClC≡CR) (RO) ₂ Mo(=NAr)=CH- <i>t</i> -Bu ((HC≡CCH ₂) ₂ C(CO ₂ Et) ₂)	Fe(acac) ₃ -Et ₃ Al (HC≡CR) [(nbd)RhCl] ₂ (HC≡CPh, HC≡CCO ₂ R)
Mechanism	Insertion	Metathesis	Metathesis	Insertion

^aHC≡CR and RC≡CR' denote mono- and disubstituted acetylenes, respectively.

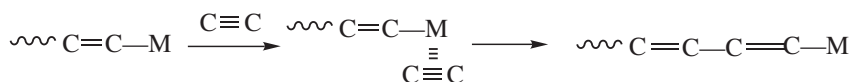
Table 3.11-2 lists typical transition metal catalysts used for the polymerization of acetylenes. It is clear that metals of various groups in the periodic table are useful. The type of monomers polymerizable with a particular catalyst is rather restricted, and hence it is important to recognize the characteristics of each catalyst. Two kinds of reaction mechanisms participate, depending on the polymerization catalysts (Scheme 3.11-2). One is the metathesis mechanism, where the active species are metal carbenes, namely, species having a metal-carbon double bond, and the other is the insertion mechanism, in which the active species are alkylmetals, namely, species having a metal-carbon single bond. These mechanisms can be distinguished from each other from the catalysts used but are rather difficult to distinguish from polymer structure.

This chapter surveys the polymerization of substituted acetylenes, focusing on the research from the 1990s up to mid-2002. Synthesis of poly(aryleneethynyls) by stepwise growth through alkyne metathesis is not discussed in this chapter. Readers are encouraged to access other reviews and monographs on the polymerization of substituted acetylenes [11–18], α,ω -diynes [19, 20], and 1,3-diacetylenes [21].

Metal carbene (metathesis) mechanism



Metal alkyl (insertion) mechanism

**Scheme 3.11-2.** Propagating species and propagation mechanisms (M: metal).

3.11.2

Polymerization Catalysts

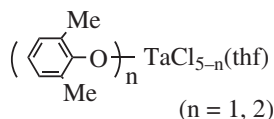
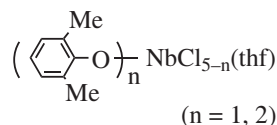
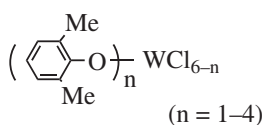
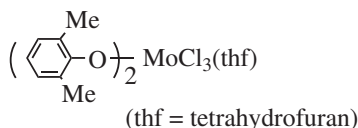
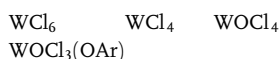
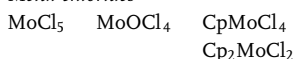
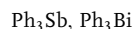
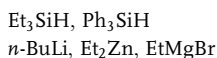
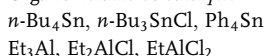
3.11.2.1

Mo and W Catalysts

These types of catalysts have been most widely employed because of their excellent ability to polymerize a wide range of substituted acetylenes [11–15, 17, 18]. These catalysts can be classified into the following three categories: metal halide-based catalysts, metal carbonyl-based catalysts, and metal-carbene catalysts.

Metal halide-based catalysts MoCl₅ and WCl₆, the most convenient group 6 transition metal catalysts, give high yield of polymers from various monosubstituted acetylenes, especially those with bulky substituents (Table 3.11-3). In the case of sterically, rather uncrowded monomers such as 1-*n*-alkyne and phenylacetylene, the yields and molecular weights of polymers are unsatisfactory ($M_n < 1 \times 10^5$) due to the unavoidable formation of cyclotrimers. In contrast, sterically demanding monomers like *tert*-butylacetylene and *ortho*-substituted phenylacetylenes selectively polymerize with MoCl₅ and WCl₆ to give high-molecular-weight polymers. MoCl₅ and WCl₆ alone are usually inactive for disubstituted acetylenes. However, appropriate organometallic co-catalysts such as *n*-Bu₄Sn, Ph₃Sn, Et₃SiH, Ph₃Sb, and Ph₃Bi remarkably activate MoCl₅ and WCl₆ catalysts and allow the effective and fast polymerization of not only mono- but also disubstituted acetylenes such as 2-octyne and 1-chloro-1-octyne.

Tab. 3.11-3. Examples of group 5 and 6 metal halide catalysts and organometallic co-catalysts.

Metal chlorides*Organometallic co-catalysts*

WCl_4 has been reported to polymerize *tert*-butylacetylene and phenylacetylene to give high-molecular-weight polymers with M_w over 1×10^5 [22]. WCl_4 becomes very active in oxygen-containing solvents such as 1,4-dioxane. A 1:2 mixture of WOCl_4 and Ph_4Sn in 1,4-dioxane/benzene solutions provides poly(phenylacetylene), whose M_w reaches 1.1×10^6 ($[\eta]$ 1.23 dl g $^{-1}$) and whose *cis* content is 73% [23]. High polymer yields can be reached irrespective of a high monomer/catalyst ratio of 1260. The viscosity index, α , of poly(phenylacetylene) has been determined to be 0.61, indicating a sufficiently flexible chain.

The catalytic activity of 2,6-dimethylphenoxo complexes of W was examined in the polymerization of 1-alkynes [24]. $\text{WCl}_{6-n}(\text{O}-2,6\text{-Me}_2\text{C}_6\text{H}_3)_n$ ($n = 1-4$) in combination with Et_3Al or EtMgBr polymerized *tert*-butylacetylene to a high-molecular-weight polymer. The complexes $\text{WCl}_5(\text{OAr})$ and $\text{WOCl}_3(\text{OAr})$, where Ar is a phenyl ligand with *o-tert*-butyl or *o*-chloro substituents, have proved to be unicomponent catalysts for the polymerization of phenylacetylene at room temperature; the M_n reaches about 1×10^5 [25].

A catalyst composed of Cp_2MoCl_2 (Cp: cyclopentadienyl) and EtAlCl_2 (1:3 mole ratio) polymerized phenylacetylene into a polymer having M_n ca. 4×10^3 [26]. A ternary catalyst, $\text{CpMoCl}_4\text{-EtMgBr-EtOH}$ (1:2:2), polymerizes *o*-CF $_3$ -phenylacetylene in a living fashion to give a polymer whose M_w/M_n is 1.06; a feature of CpMoCl_4 compared to MoOCl_4 is its higher stability to air and moisture [27].

Metal carbonyl-based catalysts Mo and W hexacarbonyls alone cause no polymerization of acetylenes. However, upon UV irradiation in halogenated solvents such as CCl_4 , various substituted acetylenes readily polymerize with Mo and W hexacarbonyls [11–15]. $\text{Cr}(\text{CO})_6$ as well as other group 7 metal carbonyls such as $\text{Mn}_2(\text{CO})_{10}$ and $\text{Re}_2(\text{CO})_{10}$ yield no active species under similar conditions. CCl_4 , used as a solvent, plays a very important role for the formation of active species and, therefore, cannot be replaced by toluene, which is often used for metal chloride-based catalysts. Although the activity of metal carbonyl-based catalysts is low compared to the metal halide-based counterparts, they provide extremely high-molecular-weight polymers. Another advantage of metal-carbonyl catalysts is their stability in air, which facilitates the experimental procedure.

The use of a catalytic amount of Ph_2CCl_2 enables the omission of CCl_4 as solvent in the metal carbonyl-catalyzed polymerization of acetylenes. For example, the polymerization of phenylacetylene with $\text{W}(\text{CO})_6$ in the presence Ph_2CCl_2 in toluene proceeds homogeneously upon photoirradiation to give a polymer with M_n of ca. 2×10^4 [28, 29]. Very high-molecular-weight polymers ($M_w > 10^5$) are attainable from sterically bulky aromatic and aliphatic acetylenes. Another extension of the $\text{M}(\text{CO})_6$ -based catalyst ($\text{M} = \text{W}, \text{Mo}$) is to use a catalytic amount of Lewis acids instead of CCl_4 [30], is also known in olefin metathesis.

An alternative metal carbonyl catalyst, $(\text{mes})\text{Mo}(\text{CO})_3$ (*mes* = mesitylene), also catalyzes the polymerization of substituted acetylenes in CCl_4 [31]. Photoirradiation is unnecessary for this system; the ligating mesitylene is readily released by heating, which allows the polymerization to proceed without photoirradiation. The

acetonitrile complexes $M(\text{CO})_3(\text{CH}_3\text{CN})_3$ ($M = \text{W}, \text{Mo}$) polymerize various mono- and disubstituted acetylenes at room temperature [32, 33]. The arene and diene complexes $(\text{mes})\text{W}(\text{CO})_3$ and $(\text{nbd})\text{Mo}(\text{CO})_3$ ($\text{nbd} = 2,5\text{-norbornadiene}$) are tolerant to polar groups such as ester, ether, and nitrile in monomers. The halogenated complex $\text{MI}_2(\text{CO})_3(\text{CH}_3\text{CN})_2$ is able to catalyze polymerization of phenylacetylene in toluene.

Another type of metal-carbonyl catalyst, $\text{MCl}_2(\text{CO})_3(\text{AsPh}_3)$ ($M = \text{Mo}, \text{W}$), that induces the ring-opening polymerization of norbornene and its derivatives has been shown to polymerize *tert*-butylacetylene and *ortho*-substituted phenylacetylenes without photoirradiation or the use of CCl_4 [34]. The reaction of *tert*-butylacetylene in the presence of seven-coordinate $\text{W}(\text{II})$ and $\text{Mo}(\text{II})$ compounds $[\text{MCl}(\text{M}'\text{Cl}_3)(\text{CO})_3(\text{NCR})_2]$ ($M = \text{Mo}, \text{W}$; $M' = \text{Sn}, \text{Ge}$; $R = \text{Me}, \text{Et}$) leads to the formation of high-molecular-weight polymer ($M_n > 10^5$) [35].

Metal carbene catalysts The first use of isolated single-component carbene catalysts showed that the Fischer (1) and Casey carbenes (2) polymerize phenylacetylene, *tert*-butylacetylene, and cyclooctyne in low yields [36] (Figure 3.11-1). For example, the bulk polymerization of *tert*-butylacetylene with 1 gives a high-molecular-weight ($M_n = 260,000$) polymer in 28% yield. Photoirradiation and/or addition of Lewis acids promote the generation of active species. As a catalyst, the Casey carbene 2 is less stable but more active than the Fischer carbene. The Rudler carbene, (3), readily releases the intramolecularly ligated double bond upon the approach of an acetylenic monomer. Thus, it is more active than the Fischer and Casey carbenes. Polymerization of 1-methoxy-1-ethynylcyclohexane and copolymerization of norbornene with *tert*-butylacetylene catalyzed by 3 have been reported [37, 38].

The polymerization chemistry of substituted acetylenes has been explosively evolved by the development of well-characterized Mo- and W-based metal carbenes, so-called Schrock carbenes, with the structure of 4. Although the preparation of these catalysts is somewhat tedious, they elegantly function as living polymerization catalysts for substituted acetylenes such as *ortho*-substituted phenylacetylenes [39, 40] and α,ω -diynes [41–43]. Since the initiation efficiency is quantitative, polymers with a desired molecular weight are available. Details for the living polymerization are described below. Polymerization of 1-octyne with 4 has been examined in detail [44].

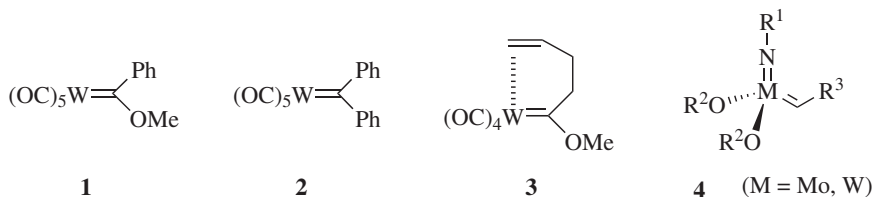


Fig. 3.11-1

3.11.2.2

Nb and Ta Catalysts

The most probable side reaction in the polymerization of acetylenes is cyclo-oligomerization that is well promoted by various transition metals including Nb and Ta. For example, cyclotrimerization of linear 1-alkynes and phenylacetylene readily occurs in the presence of NbCl_5 and TaCl_5 . Thus, bulky substituents must be incorporated into the monomers for the successful formation of polymers using Nb and Ta catalysts; in other words, these catalysts are only suited for the polymerization of disubstituted acetylenes. The simplest and most convenient catalysts are TaCl_5 and NbCl_5 (Table 3.11-3). Both catalysts can polymerize disubstituted acetylenes such as internal octynes, 1-phenyl-1-propyne, 1-trimethylsilyl-1-propyne (TMSP), and diphenylacetylenes (DPAs) [13–15].

TMSP quantitatively polymerizes with NbCl_5 and TaCl_5 alone in toluene at 80 °C to give a high-molecular-weight polymer (M_w 10^5 – 10^6) that is soluble in common solvents such as toluene and chloroform [17]. A 1:1 mixture of TaCl_5 and Ph_3Bi works as a very active catalyst for TMSP to produce a polymer whose M_w reaches 4×10^6 . This molecular weight is the highest among those of the substituted polyacetylenes ever known. The polymerization of TMSP by NbCl_5 in cyclohexane affords polymer with narrow molecular weight distribution (MWD) ($M_w/M_n \sim 1.2$) irrespective of conversion. The M_n increases in direct proportion to conversion, indicating the presence of a long-lived propagating species. Poly(TMSP) exhibits extremely high gas permeability, and hence its gas permeation behavior has been intensively studied (see below).

Although NbCl_5 and TaCl_5 alone are unable to polymerize DPA, 1:1 mixtures of TaCl_5 and suitable co-catalysts such as $n\text{-Bu}_4\text{Sn}$ and Et_3SiH afford poly(DPA) in good yield. Poly(DPA) is thermally very stable (stable up to ca. 500 °C) but is insoluble in any solvent. The derivatives of DPA having $p\text{-Me}_3\text{Si}$, $p\text{-}t\text{-Bu}$, $n\text{-Bu}$, $p\text{-PhO}$, and $p\text{-}N\text{-carbazolyl}$ groups polymerize in a similar way in the presence of TaCl_5 – $n\text{-Bu}_4\text{Sn}$ catalyst [45, 46]. These polymers are totally soluble in toluene and other common solvents and have high molecular weights of around 1×10^6 .

There has been a demonstration of the unique ability of 2,6-dimethylphenoxo (dmp) complexes of Nb, **5**, with co-catalysts such as EtMgBr or Et_3Al , to polymerize terminal acetylenes such as *tert*-butylacetylene and phenylacetylene into high-molecular-weight polymers [24] (Figure 3.11-2). The exceptional ability of the **5** co-catalyst system originates from the presence of bulky aryloxo groups that have the

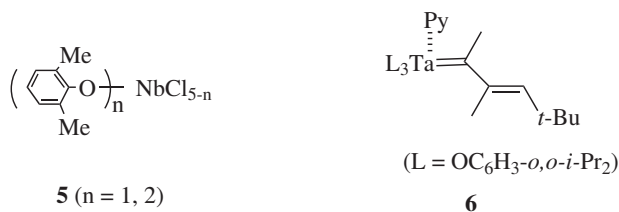


Fig. 3.11-2

same effect as bulkiness on the monomer. Ta carbene **6** induces living polymerization of 2-butyne (see below) [47].

3.11.2.3

Rh Catalysts

Rh catalysts are now known to polymerize substituted acetylenes such as phenylacetylene, propiolic acid esters, and *N*-propargylalkylamides. Rh-catalyzed polymerizations proceed by the insertion mechanism [16, 18, 33, 48]. The most characteristic feature of Rh catalysts is their very high activity for the polymerization of phenylacetylenes to give high-molecular-weight polymers with almost perfect stereoregularity (*cis-transoidal*). Furthermore, the excellent ability of Rh catalysts to tolerate various functional groups, such as amino, hydroxyl, azo, and radical groups, allows the synthesis of highly functionalized polymers.

Dinuclear Rh complexes such as $[(nbd)RhCl]_2$ (**7**) and $[(cod)RhCl]_2$ (*cod* = 1,5-cyclooctadiene) [16] and cationic Rh complexes such as $(nbd)Rh^+[(\eta^6-C_6H_5)B^-(C_6H_5)_3]$ (**8**) [49] have frequently been employed for the polymerization of phenylacetylenes (Figure 3.11-3). $[(nbd)RhCl]_2$ is usually more active and stable than $[(cod)RhCl]_2$. The most widely applied catalyst is $[(nbd)RhCl]_2-Et_3N$ [50, 51]. This catalyst gives excellent yields of stereoregular poly(phenylacetylene) with high molecular weight ($M_n > 10^5$). Combinations of $[(nbd)RhCl]_2$ with suitable organometallics such as *n*-BuLi and Et_3Al greatly accelerate the polymerization of phenylacetylene [52]. Living polymerization of phenylacetylene is feasible by using a well-characterized Rh complex, $(nbd)(PhC\equiv C)Rh(PPh_3)_2$ (**9**), in conjunction with 4-(dimethylamino)pyridine [53–56]. An extension of this system is a multi-component catalyst, $[(nbd)RhOCH_3]_2-PPh_3-4-(dimethylamino)pyridine$ [57]. A ternary Rh catalyst system, $[(nbd)RhCl]_2-LiCPh=CPh_2-PPh_3$ [58, 59], has proven to induce the living polymerization of phenylacetylenes. In the latter case, the initiating species is a vinylrhodium (**10**), which was isolated and characterized by X-ray analysis [60]. Details for the living polymerization are described in the next section.

The Rh-catalyzed polymerization proceeds in various solvents such as benzene, tetrahydrofuran, ethanol, and triethylamine [16, 50]. Among the solvents, ethanol and triethylamine are favorable for phenylacetylenes from the viewpoint of both polymerization rate and polymer molecular weight. Polymerization of phenyl-

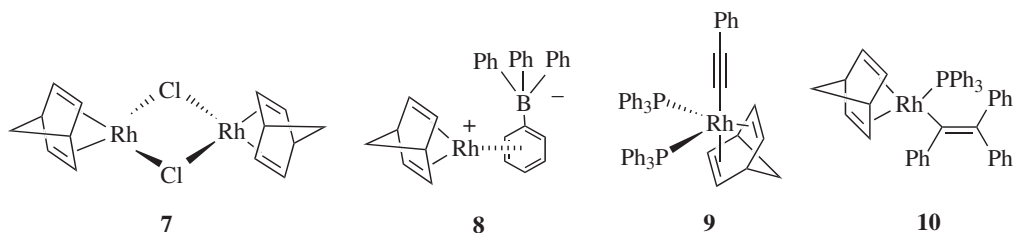
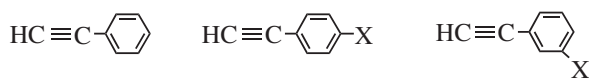


Fig. 3.11-3

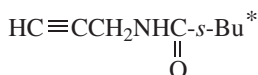
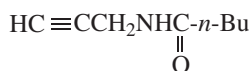
acetylenes is feasible even in aqueous media using water-soluble catalysts. For example, $(\text{cod})\text{Rh}^+(\text{mid})_2\text{PF}_6^-$ ($\text{mid} = N\text{-methylimidazole}$) provides *cis*-transoidal poly(phenylacetylene) (*cis* 98%) in high yield (98%) [61]. Other catalysts, such as $(\text{cod})\text{Rh}(\text{SO}_3\text{C}_6\text{H}_4\text{-}p\text{-CH}_3)(\text{H}_2\text{O})$ and $(\text{nbd})\text{Rh}(\text{SO}_3\text{C}_6\text{H}_4\text{-}p\text{-CH}_3)(\text{H}_2\text{O})$, also work as water-soluble catalysts. Polymerization of phenylacetylene in compressed (liquid or supercritical) CO_2 has been studied using a Rh catalyst, $[(\text{nbd})\text{Rh}(\text{acac})_2]$ [62]. A higher polymerization rate is obtained in CO_2 than in conventional organic solvents such as THF and hexane. Quite recently, ionic liquids have been examined as media for Rh-catalyzed polymerization of phenylacetylene [63].

Although practically only phenylacetylene and its *para*- and *meta*-substituted derivatives [16, 64] were used previously as monomers in the Rh-catalyzed polymerization, various new monomers have been examined recently (Table 3.11-4). For instance, several alkyl propiolates polymerize in moderate yields with Rh catalysts [65]. Relatively high yields of poly[(-)-menthyl propiolate] with high molecular weights are accessible when the polymerization is conducted in alcohols or acetonitrile at high monomer and catalyst concentrations [66]. A characteristic feature of the polymers formed from alkyl propiolates is their almost perfect *cis*-stereoregularity, and eventually they exist in a well-ordered helical conformation (see below for details on the synthesis of helical polyacetylenes [48, 67, 68]). Although carboxylic acids are known to serve as terminator, sodium *p*-ethynylphenylcarboxylate and propiolate polymerize in the presence of various cationic Rh complexes [69, 70]. Recently it has been found that *N*-propargylalkylamides polymerize with Rh complex **8** to produce helical polymers. The helicity of these polymers is induced not by steric effect but by hydrogen bonding (see below for details) [71, 72]. In general, Rh catalysts are not very effective for sterically crowded

Tab. 3.11-4. Examples of the monomers polymerizable with Rh catalysts.



(X = Me, OMe, Cl, COOR, COOCPh₃, etc)



monosubstituted acetylenes such as *tert*-butylacetylene and *ortho*-substituted phenylacetylenes. Disubstituted acetylenes cannot be polymerized with Rh catalysts. Only one exceptional example has been found by using cyclooctyne as a monomer; its very large ring strain ($\sim 38 \text{ kJ mol}^{-1}$) enables rapid polymerization with $[(\text{nbd})\text{RhCl}]_2$, giving an insoluble polymer in good yield [73].

3.11.2.4

Other Group 8–10 Metal Catalysts

Iron-based heterogeneous Ziegler-type catalysts such as $\text{Fe}(\text{acac})_3\text{--Et}_3\text{Al}(1:3)$ (acac = acetylacetonate) have been known for a long time, are readily prepared *in situ*, and are able to polymerize sterically unhindered terminal acetylenes such as *n*-alkyl-, *sec*-alkyl-, and phenylacetylenes [15, 18]. The poly(phenylacetylene) formed has a red color and a *cis*-cisoidal structure and is insoluble and crystalline.

Group 10 transition metal catalysts including Ni and Pd, which often induce cyclic and linear oligomerization of acetylenes, have not been studied in detail with respect to their polymerization, and hence only fragmental information is available about the catalyst/monomer relationship. Polymerization of *N,N*-dimethylpropargylamine and ethynylpropargylsilane with $\text{Ni}(\text{NCS})_2\text{PPh}_3$ [74] and $[\text{Pd}(\text{C}\equiv\text{CR})_2(\text{PPh}_3)_2]$ ($\text{R} = \text{SiMe}_3, \text{CH}_2\text{OH}, \text{CH}_2\text{NMe}_2$) [75], respectively, provides insoluble metal-coordinated conjugated polymers. 2-, 3-, and 4-Nitrophenyl propargyl ethers polymerize with PdCl_2 in DMF, giving soluble brown polymers that show broad MWD with peak tops at 4×10^3 and 1×10^5 [76]. On the other hand, 3-diethylaminophenyl propargyl ether affords a low-molecular-weight ($M_n \sim 4 \times 10^3$) soluble polymer. Poly(cyanoacetylene) has been prepared from the corresponding monomer using a variety of Pd and Ni catalysts such as $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ and $(\text{Ph}_3\text{P})_2\text{NiCl}_2$ [77]. The formed polymers have M_w of around 1×10^4 and always contain catalyst metals according to elemental analysis. The catalyst system $\text{Ni}(\text{cod})_2\text{--CF}_3\text{COO}(\text{allyl})$ polymerizes phenylacetylene into a polymer of M_n 12,000 in good yield [78]. Cyclopentadienylnickel complexes produce a mixture of polymer ($M_n \sim 3 \times 10^3$) and linear and cyclic oligomers [79].

3.11.3

Controlled Polymerizations

An important subject in polymer synthesis is the control of polymerization to prepare polymers having precise structures. Living polymerization and stereospecific polymerization are two important methods of controlling polymer structure. The π -conjugated polymers prepared by the sequential polymerization are strictly limited to polyacetylenes, except for a few examples. Thus, synthesis of tailor-made conjugated macromolecules such as end-functionalized polymers, block copolymers, and star-shaped polymers is possible only in the case of substituted acetylenes. Diverse transition metals from group 3 to 10 elements initiate the polymerization of substituted acetylenes. Catalysts that achieve living polymerization,

however, are quite limited, compared to the wide variety of living polymerization catalysts for vinyl monomers. The catalysts are classified into the following groups: (1) metal halide-based catalysts, (2) metal carbenes, and (3) Rh complexes. The structure of monomers undergoing living polymerization significantly depends on the type of catalyst. Thus, appropriate catalysts must be selected in order to synthesize well-defined polymers from the individual monomers. Table 3.11-5 shows typical examples of the living polymerization of substituted acetylenes.

3.11.3.1

Living Polymerization by Metal Halide-Based Metathesis Catalysts

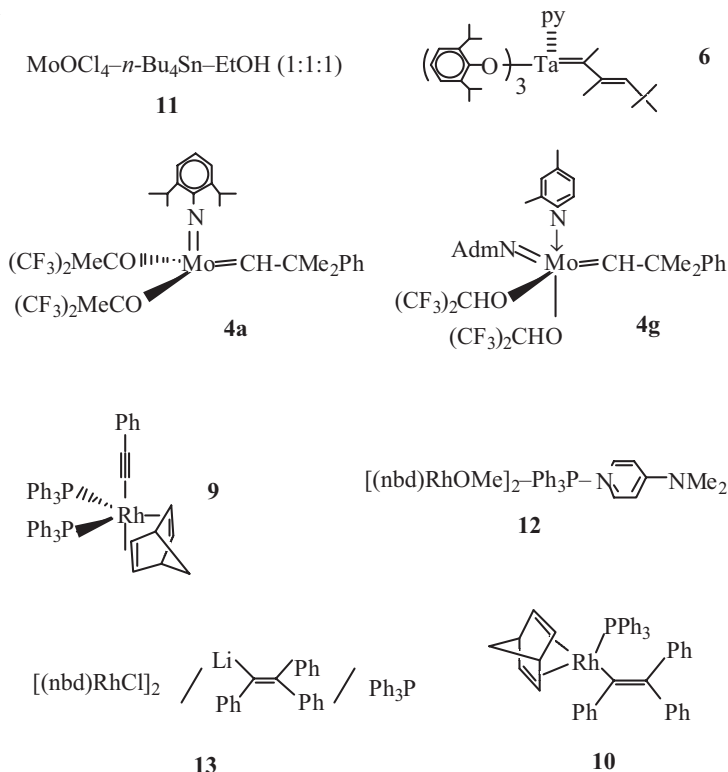
The general formula of metal halide-based living polymerization catalysts is expressed as $\text{MO}_n\text{Cl}_m\text{-co-catalyst-ROH}$ ($\text{M} = \text{Mo}$ or W , $n = 0$ or 1 , $m = 5$ or 4) [15, 45]. The most important feature of these catalysts is the ease of preparation, while its weak point is that as a living polymerization, the initiation efficiency is not quantitative. The living polymerization of substituted acetylenes has been achieved, for the first time, in the polymerization of 1-chloro-1-octyne with $\text{MoCl}_5\text{-}n\text{-Bu}_4\text{Sn-EtOH}$ [80]. Namely, poly(1-chloro-1-octyne) with narrow MWD ($M_w/M_n < 1.2$) was obtained, and the living nature was confirmed by the linear dependence of molecular weight on monomer conversion and by the successful initiation of the polymerization of second-charged monomers with the living prepolymer. The use of MoOCl_4 instead of MoCl_5 provides propagation species with a longer lifetime [81]. Thus, the most efficient catalyst of this group is $\text{MoOCl}_4\text{-}n\text{-Bu}_4\text{Sn-EtOH}$, which has been employed most frequently.

The ternary $\text{MoOCl}_4\text{-}n\text{-Bu}_4\text{Sn-EtOH}$ catalyst induces living polymerization of not only 1-chloro-1-alkynes but also phenylacetylenes with bulky *ortho*-substituents [82–84]. The presence of bulky *ortho*-substituents (e.g., CF_3 , SiMe_3 , GeMe_3 , etc.) is essential to achieve excellent living polymerization, probably because *ortho*-substituents are able to sterically preclude chain transfer and termination. Thus, the living nature of (*o*-methylphenyl)acetylene is slightly low [87]. It is interesting to note that a phenylacetylene derivative, *p*-Bu-*o,o,m,m*-F₄-phenylacetylene, which has two medium-sized *ortho*-substituents, also yields a polymer with low polydispersity [85]. Apart from 1-chloro-1-alkynes, the following disubstituted acetylenes also polymerize in a living fashion with the $\text{MoOCl}_4\text{-}n\text{-Bu}_4\text{Sn-EtOH}$ catalyst: internal alkynes (e.g., 2-nonyne, 3-nonyne) [88], 1-chloro-2-phenylacetylene [89], and diethyl di-2-butyryl malonate $[(\text{EtO}_2\text{C})_2\text{C}(\text{CH}_2\text{C}\equiv\text{CMe})_2]$ [90]. Stereospecific living polymerization of *tert*-butylacetylene is possible with $\text{MoOCl}_4\text{-}n\text{-Bu}_4\text{Sn-EtOH}$, which gives a polymer with a narrow MWD [86]. The *cis* content reaches 97% at low temperature (-30°C) and decreases when the polymerization is conducted with MoOCl_4 or $\text{MoOCl}_4\text{-}n\text{-Bu}_4\text{Sn}$. A detailed NMR study on the stereoregularity of poly(*tert*-butylacetylene) showed that the *cis* content depends on the rate of Lewis-acid-catalyzed isomerization from the *cis* to the *trans* form [91].

Although toluene is a useful polymerization solvent, anisole gives better results, i.e., it achieves narrower MWD and higher initiation efficiency, which is attributed to its slightly basic and polar properties [92]. Not only *n*-Bu₄Sn but also a variety of

Tab. 3.11-5. Living polymerization of substituted acetylenes.

Monomer	Catalyst ^a	$\frac{M_w}{M_n}$	Ref.
$\text{ClC}\equiv\text{C}-n\text{-C}_6\text{H}_{13}$	11	1.13	80, 81
$\text{HC}\equiv\text{CC}_6\text{H}_4\text{-}o\text{-CF}_3$	11	1.06	82
$\text{HC}\equiv\text{CC}_6\text{H}_4\text{-}o\text{-SiMe}_3$	11	1.07	83
$\text{HC}\equiv\text{CC}_6\text{H}_4\text{-}o\text{-GeMe}_3$	11	1.08	84
$\text{HC}\equiv\text{CC}_6\text{F}_4\text{-}p\text{-Bu}$	11	1.16	85
$\text{HC}\equiv\text{C}-t\text{-Bu}^b$	11	1.12	86
$\text{MeC}\equiv\text{CMe}$	6	1.03	47
$(\text{HC}\equiv\text{CCH}_2)_2\text{C}(\text{CO}_2\text{Et})_2$	4a	~1.20	41–43
$\text{HC}\equiv\text{CC}_6\text{H}_4\text{-}o\text{-SiMe}_3$	4g	1.05	39
$\text{HC}\equiv\text{CPh}^c$	9	1.15	53–56
$\text{HC}\equiv\text{CPh}^c$	12	1.11	57
$\text{HC}\equiv\text{CPh}^c$	13	1.14	58, 59
$\text{HC}\equiv\text{CPh}^c$	10	1.05	60

^a^b Stereoregular (*cis* 97%) and living polymer is formed.^c Stereoregular (all *cis*) and living polymers are formed.

other organometallic compounds such as Et_3Al [93, 94], Et_2Zn [95], and $n\text{-BuLi}$ [96, 97] can be used as co-catalysts. It is interesting that the addition of the third component, the protic additive, is not necessary in the case of $n\text{-BuLi}$. Variation of co-catalysts affects the initiation efficiency and block copolymerization behavior. Initiation efficiency decreases in the order of $n\text{-Bu}_4\text{Sn} > \text{Et}_3\text{Al} > \text{Et}_2\text{Zn} > n\text{-BuLi}$. Consequently, extremely high-molecular-weight polymers ($>10^5$) with very narrow MWD (<1.03) are attainable by using $\text{MoOCl}_4\text{-}n\text{-BuLi}$ [96]. Tungsten-based multi-component catalysts, $\text{WOCl}_4\text{-}n\text{-Bu}_4\text{Sn-}t\text{-BuOH}$, $\text{WOCl}_4\text{-}n\text{-BuLi}$, and $\text{WOCl}_4\text{-EtMgBr}$ have been proven to achieve controlled polymerizations of $o\text{-CF}_3\text{-phenylacetylene}$, $o\text{-Me}_3\text{Si-phenylacetylene}$, $p\text{-Bu-}o,o,m,m\text{-F}_4\text{-phenylacetylene}$, 3-decyne, and 5-dodecyne [98, 99].

By the sequential living polymerization using the $\text{MoOCl}_4\text{-}n\text{-Bu}_4\text{Sn-EtOH}$ catalyst, diblock copolymers with very narrow MWD have been selectively formed from any combinations of two monomers selected from 1-chloro-1-octyne, $o\text{-Me}_3\text{Si-phenylacetylene}$, and $o\text{-CF}_3\text{-phenylacetylene}$, irrespective of the order of monomer addition [100]. Further, this catalyst enabled us to produce ABC- and ABA-type triblock copolymers from these three monomers. Several diblock copolymers with much higher molecular weights are obtained with the $\text{MoOCl}_4\text{-Et}_3\text{Al-EtOH}$ and $\text{MoOCl}_4\text{-}n\text{-BuLi}$ catalysts, owing to lower initiation efficiencies. 1-Chloro-2-phenylacetylene, 2-nonyne, and $p\text{-Bu-}o,o,m,m\text{-F}_4\text{-phenylacetylene}$ can also be used as comonomers to prepare block copolymers with the above-stated monomers [101].

3.11.3.2

Living Polymerization by Single-Component Metal-Carbene Catalysts

Mo-carbene catalysts **4a–d** have been synthesized (Figure 3.11-4) and have proven to elegantly induce living cyclopolymerization of 1,6-heptadiynes [41, 42]. Mo car-

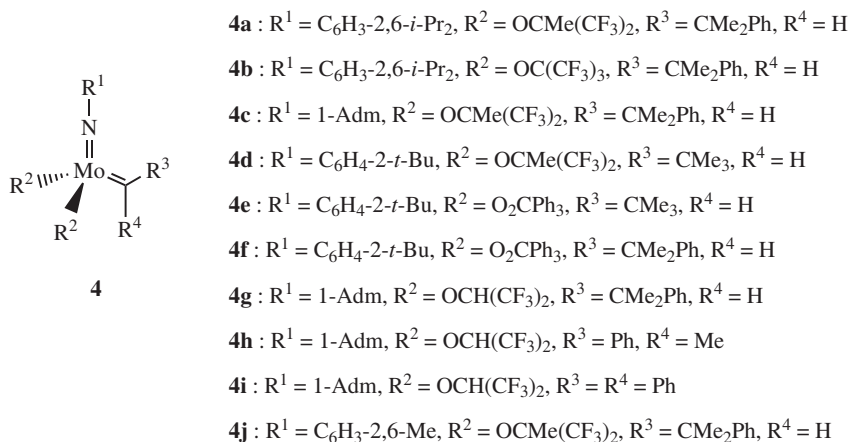


Fig. 3.11-4

benes ligated by bulky imido and alkoxy groups are quite effective. Because there is no significant difference between the propagation and initiation rates, the resultant polymers show relatively broad MWD ($M_w/M_n \sim 1.25$). The ability of these Mo carbenes to tolerate polar functional groups permits living polymerization of functionalized monomers containing ester, sulfonic ester, and siloxy groups. End capping of the polymers is readily accomplished by using aromatic aldehydes including *p*-*N,N*-dimethylaminobenzaldehyde and *p*-cyanobenzaldehyde. Cyclopolymerization of 1,6-heptadiynes with **4a–d** offers polymers having both 5- and 6-membered cyclic structures. In contrast, **4e** and **4f**, which have bulky carboxylate ligands, produce polymers bearing only 6-membered rings [43].

Ring-substituted phenylacetylenes have been adopted in the Mo carbene-initiated polymerization, leading to a finding that well-defined polymers are readily obtained with Mo carbenes **4g–i** ligated by less bulky alkoxy groups [39, 40]. Because of their instability, isolation of **4g–i** cannot be accomplished unless an appropriate base is added. As in metal halide-induced living polymerizations, bulky ring substituents at the *ortho* position are required for controlled polymerization. The most characteristic point of these polymerization systems is that all the steps, including initiation and propagation, can be readily monitored by an NMR techniques. Eventually, it was found that the alkylidene groups of **4** selectively undergo α -addition onto *o*-Me₃Si-phenylacetylene, whereas the selectivity of α -addition decreases with the decrease in the bulkiness of *ortho* substituents.

The metal-containing monomers ferrocenylacetylene and ruthenocenylacetylene have been subjected to living polymerization with Mo carbene **4j**, which has bulky alkoxide ligands [102]. Living polymers are inaccessible with **4g–i**, which are useful for *ortho*-substituted phenylacetylenes. Due to the poor solubility of these polymers, the degree of polymerization must be restricted below ca. 40 in order to produce soluble polymers. Similar metallocene-containing monomers, such as HC≡CC₆H₄-*o*-Fc (Fc = ferrocenyl), HC≡CC₆H₄-*p*-CH=CHFc, HC≡CC₆H₄-*p*-N=Nf, and HC≡CC₆H₄-*p*-C≡CC₆H₄-*p*-C≡CFc, polymerize in a living manner in the presence of **4j** [103, 104].

In addition to these Mo- and W-based carbene complexes, a Ta carbene (**6**) that is active for the living polymerization of 2-butyne has been developed [47]. Again, the initiation efficiency is quantitative, and the living end can be end capped with aromatic aldehydes. Because polymers from symmetric acetylenes are generally insoluble, soluble poly(2-butyne) is only accessible if the degree of polymerization is suppressed below 200. NMR analysis of living oligomers of 2-butyne clearly indicates that both *cis* and *trans* structures exist in the main chain.

3.11.3.3

Stereospecific Living Polymerization by Rh Catalysts

Rh-catalyzed living polymerization was first accomplished in 1994 [53]. The excellent ability of an isolated catalyst (**9**) to offer quantitative yields of poly(phenylacetylenes) with narrow MWD was demonstrated. The structure of **9** was completely characterized by a single-crystal X-ray analysis, and it has been

disclosed that the initiation reaction proceeds not *via* direct insertion of monomer into **9** but through the formation of a Rh–H complex by the reaction of **9** with the monomer followed by monomer insertion [56]. Polymerization of phenylacetylene with **9** in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) provides a well-defined polymer having a long-lived active site at the propagation terminal. DMAP is indispensable, and without it, the polydispersity increases to 1.3. High stability of the propagation centers allows the isolation of poly(phenylacetylene) having active propagation sites that can sequentially polymerize different monomers to give precisely controlled block copolymers.

One striking feature of the stereoregular polyacetylenes is their simple NMR spectral patterns, which facilitate investigation of the polymerization mechanism as well as of the polymer structure. A copolymer of phenylacetylene with partly ^{13}C -labeled phenylacetylene ($\text{Ph}^{13}\text{C}\equiv^{13}\text{CH}$) shows two doublet carbon signals with $J_{^{13}\text{C}-^{13}\text{C}}$ of 72 Hz, indicating the presence of a $^{13}\text{C}=\text{C}$ bond in the polymer backbone [56]. This is a clear indication of the insertion mechanism instead of a metathesis pathway.

After the discovery of catalyst **9**, further development of a new living polymerization system, $[(\text{nbd})\text{RhOMe}]_2\text{-Ph}_3\text{P-DMAP}$, has enabled enhancement of the initiation efficiency to 70% from 35% [57]. The polymerization with $[(\text{nbd})\text{Rh}(\text{OCH}_3)]_2\text{-Ph}_3\text{P-DMAP}$ is three to four times faster than that with **9**. The isolation of $[(\text{nbd})\text{RhOMe}]_2$ is not necessary; a simple mixture of commercially available $[(\text{nbd})\text{RhCl}]_2$, Ph_3P , NaOMe , and DMAP induces the living polymerization of phenylacetylene without broadening the polydispersity.

A new vinylrhodium complex (**10**) for the living polymerization of phenylacetylenes has been prepared, isolated, and fully characterized by X-ray analysis [60]. Catalyst **10** polymerizes phenylacetylene and its *para*-substituted analogues to give living polymers. Living polymerization is also possible even in the presence of water. The isolation of **10** is not necessary, and the complex formed *in situ* by the reaction of $[(\text{nbd})\text{RhCl}]_2$ with $\text{LiCPh}=\text{CPh}_2$ and Ph_3P induces living polymerization with quantitative initiation efficiency [58]. A remarkable feature of this polymerization system is the ability to introduce functional groups at the initiation terminal. For example, living poly(phenylacetylene) bearing a terminal hydroxyl group is readily obtained by the polymerization with a three-component catalyst, comprising $[(\text{nbd})\text{RhCl}]_2$, $\text{LiCPh}=\text{C}(\text{Ph})(\text{C}_6\text{H}_4\text{-}p\text{-OSiCH}_3\text{-}t\text{-Bu})$, and Ph_3P , followed by the desilylation of the formed polymer. Polymerization of β -propiolactone with the terminal phenoxide anion of this polymer gives a new block copolymer of phenylacetylene with β -propiolactone [105].

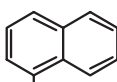
3.11.4

New Monomers and Functional Polymers

Table 3.11-6 lists examples of the polymerization of substituted acetylenes that have been reported since the early 1990s. This table will help readers to understand the relationship between monomer structure and catalyst type and to list new

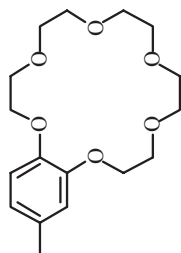
Tab. 3.11-6. Polymerization of substituted acetylenes with transition metal catalysts.

Monomer	Catalyst	$M_n/10^3$	Ref.
[A] Monosubstituted aliphatic acetylenes [HC≡CR] R = 1-Cyclohexenyl			
	[(nbd)RhCl] ₂ -Et ₃ N	24	106
	MoOCl ₄ -Me ₄ Sn	350	107
	MoCl ₅ -EtAlCl ₂	480	
	Fe(acac) ₃ -Et ₃ Al	610	108
	MoCl ₅ -Ph ₄ Sn	15	108
	[(nbd)RhCl] ₂ -Et ₃ N	96	109
	Fe(acac) ₃ -Et ₃ Al	121	109
	WCl ₆ -Ph ₄ Sn	14	110
	{[Mo{OC(Me)(CF ₃) ₂] ₂] ₂ =N(2,6-Me ₂ C ₆ H ₃)=CHCMe ₂ Ph} (4j)	40	111
	(nbd)Rh ⁺ [(<i>η</i> ⁶ -C ₆ H ₅)B ⁻ (C ₆ H ₅) ₃]	28	112
	[(nbd)RhCl] ₂	20	65
	[(Cp ⁺)RuCl] ₂	4	113
	[(nbd)RhCl] ₂	250	66
	MoOCl ₄ - <i>n</i> -Bu ₄ Sn	18	66

CH ₂ OH					
(CH ₂) ₁₀ OH					
CN					
CH ₂ N(CH ₃) ₂					
CH ₂ -N-indolyl					
CH ₂ CH(CO ₂ C ₂ H ₅)PO(OC ₂ H ₅) ₂					
CH ₂ ⁺ PPh ₃ BPh ₄ ⁻					
[B] Monosubstituted aromatic acetylenes					
$\left[\text{HC} \equiv \text{C} - \langle \text{C}_6\text{H}_4 \rangle - \text{R} \right]$					
Phenylacetylenes					
R = <i>p</i> -Adm					
<i>o,o'</i> -(CH ₃) ₂ - <i>p-t</i> -Bu					
<i>p</i> -OCH ₃					
<i>p</i> -Cl					
<i>p</i> -NO ₂					
<i>m</i> -CH=NPh					
<i>p</i> -I					
<i>p</i> -CO ₂ CH ₃					
<i>p</i> -CO ₂ (CH ₂) ₂ O-C ₆ H ₄ -CN					
<i>p</i> -CO ₂ (CH ₂) ₆ O ₂ C-C ₆ H ₄ -OC ₇ H ₁₅					
<i>p</i> -CO ₂ (-)-Menthyl					
<i>p</i> -OCONHC*H(CH ₃)Ph					
<i>p</i> -OCONHC*H(CH ₃)- 					
CH ₂ OH	53				114
(nbd)Rh ⁺ [(η ⁶ -C ₆ H ₅)B ⁻ (C ₆ H ₅) ₃]	32				115
(Ph ₃ P) ₂ NiCl ₂	9				77
Pd(PPh ₃) ₂ [C≡CCH ₂ N(CH ₃) ₂]	15				114
[(nbd)RhCl] ₂ -Et ₃ N	71				116
WCl ₆ -EtAlCl ₂	9				117
MoCl ₅ -Ph ₄ Sn	12				118
[(nbd)RhCl] ₂ -Et ₃ N					119
W(CO) ₆ -CCl ₄ -hν	>1000				120
[(nbd)RhCl] ₂ -Et ₃ N	2600(M _w)				51
[(nbd)RhCl] ₂ -Et ₃ N	60(M _w)				51
[(cod)RhCl] ₂	260(M _w)				121
[(nbd)RhCl] ₂ -Et ₃ N	15.5				122
WOC ₄	588				123
(nbd)Rh ⁺ [(η ⁶ -C ₆ H ₅)B ⁻ (C ₆ H ₅) ₃]	19				49
[(nbd)RhCl] ₂ -Et ₃ N	218				124
[(nbd)RhCl] ₂ -Et ₃ N	158				125
[(nbd)RhCl] ₂ -Et ₃ N	122				126
[(nbd)RhCl] ₂ -Et ₃ N	1260				127
[(nbd)RhCl] ₂ -Et ₃ N	320				128
[(nbd)RhCl] ₂ -Et ₃ N	51				128

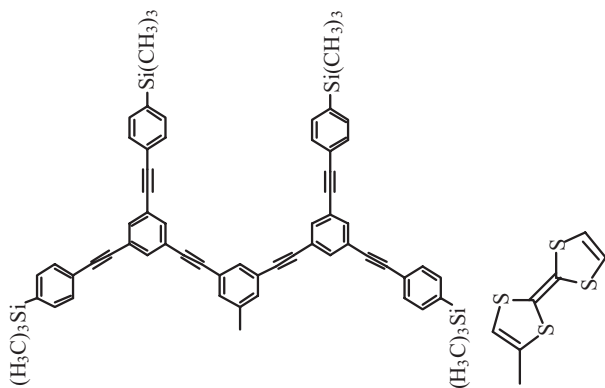
Tab. 3.11-6. (continued)

Monomer	Catalyst	$M_n/10^3$	Ref.
$p\text{-CH}_2\text{NHC}^+\text{H}(\text{CH}_3)\text{C}^+\text{H}(\text{OH})\text{Ph}$	$[(\text{nbdt})\text{RhCl}]_2$	48	129
$p\text{-N}(n\text{-C}_4\text{H}_9)_2$	$[(\text{nbdt})\text{RhCl}]_2\text{-Et}_3\text{N}$	>1000	130
$p\text{-N}(i\text{-C}_3\text{H}_7)_2$	$[(\text{nbdt})\text{RhCl}]_2\text{-Et}_3\text{N}$	—	131
$2,5\text{-(CF}_3)_2$	$\text{W}(\text{CO})_6\text{-CCl}_4\text{-h}\nu$	$[\eta] = 0.352$	132
$o\text{-Si}(\text{CH}_3)_3$	$\text{W}(\text{CO})_6\text{-CCl}_4\text{-h}\nu$	$1200(M_w)$	133
$o\text{-Ge}(\text{CH}_3)_3$	WCl_6	$690(M_w)$	134
$p\text{-(=Si-}i\text{-Pr}_3)$	$[(\text{cod})\text{Rh}(\mu\text{-OMe})]_2$	24	135
$o,o,m,m,p\text{-F}_5$	$\text{WCl}_6\text{-Ph}_4\text{Sn}$		136
$o,o,m,m,F_4\text{-}p\text{-}n\text{-Bu}$	$\text{WCl}_6\text{-Ph}_4\text{Sn}$	$[\eta] = 0.61$	137
$m\text{-N=NPh}$	$[(\text{nbdt})\text{RhCl}]_2\text{-Et}_3\text{N}$	110	137
$p\text{-N=NPh}$	$[(\text{nbdt})\text{RhCl}]_2\text{-Et}_3\text{N}$	110	138
$p\text{-N=NPh-}p\text{-Me}$	$[(\text{cod})\text{RhCl}]_2$	20	139
$o\text{-Fc}$	4a	9	140
$p\text{-CH=CHFc}$	4j	16	103
$p\text{-N=NFc}$	4j	19	103
$p\text{-C}\equiv\text{CC}_6\text{H}_4\text{-}p\text{-C}\equiv\text{CFc}$	4j	11	103
	4j	18	104
	$\text{WOCl}_4\text{-Me}_4\text{Sn}$		141
Other aromatic acetylenes [$\text{HC}\equiv\text{CAr}$]			
Ar = 1-Naphthyl			
1-Anthryl	$\text{WCl}_6\text{-Ph}_3\text{Bi}$	46	142
2-Anthryl	$\text{WCl}_6\text{-Ph}_4\text{Sn}$	37	143
9-Anthryl	$\text{WCl}_6\text{-Ph}_4\text{Sn}$	9	143
2-Phenanthryl	WCl_6	Insoluble	142
3-Phenanthryl	$\text{WCl}_6\text{-Ph}_3\text{Bi}$	10	143
1-Pyrenyl	$\text{WCl}_6\text{-Ph}_3\text{Bi}$	24	143
N-Carbazolyl	$\text{WCl}_6\text{-Ph}_3\text{Bi}$	6	144
	$\text{WCl}_6\text{-}n\text{-Bu}_4\text{Sn}$	13	145


 $[(\text{nbd})\text{RhCl}]_2\text{-Et}_3\text{N}$

26

146


 $[(\text{nbd})\text{RhCl}]_2\text{-Et}_3\text{N}$

340


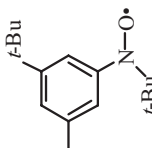
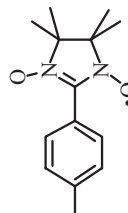

147

 $[(\text{nbd})\text{RhCl}]_2\text{-Et}_3\text{N}$


11.7

148

Tab. 3.11-6. (continued)

Monomer	Catalyst	$M_n/10^3$	Ref.
	$[(\text{cod})\text{RhCl}]_2$	95.3	149
	$[(\text{nbd})\text{RhCl}]_2\text{-Et}_3\text{N}$	11	150
	$(\text{cod})\text{Rh}(\text{NH}_3)\text{Cl}$	150	151
Ferrocenyl $[(\eta^6\text{-C}_5\text{H}_4)_2\text{Fe}(\eta^6\text{-C}_5\text{H}_5)]$ Ruthenocenyl $[(\eta^6\text{-C}_5\text{H}_4)_2\text{Ru}(\eta^6\text{-C}_5\text{H}_5)]$ [C] Disubstituted aliphatic acetylenes $[\text{R}^1\text{C}\equiv\text{CR}^2]$ $\text{R}^1 = \text{CH}_3$ $\text{R}^2 = \text{S-}n\text{-C}_4\text{H}_9$	$\text{Mo}[\text{OC}(\text{Me})(\text{CF}_3)_2]_2 = \text{N}(2,6\text{-Me}_2\text{C}_6\text{H}_3) = \text{CHCMe}_2\text{Ph}$ (4j) $\text{Mo}[\text{OC}(\text{Me})(\text{CF}_3)_2]_2 = \text{N}(2,6\text{-Me}_2\text{C}_6\text{H}_3) = \text{CHCMe}_2\text{Ph}$ (4j)	16.4 16	102 102
	$\text{MoCl}_5\text{-Ph}_3\text{SiH}$	71	152
CH_3	$\text{TaCl}_5\text{-Ph}_3\text{Bi}$	80	153
 CH_3 $\text{Ge}(\text{CH}_3)_3$	TaCl_5	809	154

[D] Disubstituted aromatic acetylenes [RC≡CAr]

R = Cl	Ar = C ₆ H ₄ , <i>p</i> -Adm			
Ph	C ₆ H ₄ , <i>p</i> - <i>n</i> -C ₄ H ₉	MoCl ₅ - <i>n</i> -Bu ₄ Sn	110	155
Ph	C ₆ H ₄ , <i>p</i> - <i>t</i> -Bu	TaCl ₅ - <i>n</i> -Bu ₄ Sn	460	156
Ph	C ₆ H ₄ , <i>p</i> -Adm	TaCl ₅ - <i>n</i> -Bu ₄ Sn	1400	156
Ph	C ₆ H ₄ , <i>p</i> -Ph	TaCl ₅ - <i>n</i> -Bu ₄ Sn	2200	155
Ph	C ₆ H ₄ , <i>p</i> -CH ₂ Ph	TaCl ₅ - <i>n</i> -Bu ₄ Sn	Insoluble	157
Ph	C ₆ H ₄ , <i>p</i> -OPh	TaCl ₅ - <i>n</i> -Bu ₄ Sn	350	157
Ph	C ₆ H ₄ , <i>p</i> -OC(CF ₃)=C[CF(CF ₃) ₂] ₂	TaCl ₅ - <i>n</i> -Bu ₄ Sn	1700	158
Ph	C ₆ H ₄ , <i>p</i> -N-Carbazolyl	TaCl ₅ - <i>n</i> -Bu ₄ Sn	[η] = 0.87	159
Ph	C ₆ H ₄ , <i>p</i> -Si(CH ₃) ₃	TaCl ₅ - <i>n</i> -Bu ₄ Sn	190	160
Ph	C ₆ H ₄ , <i>p</i> -SiPh ₃	TaCl ₅ - <i>n</i> -Bu ₄ Sn	750	161, 162
Ph	<i>p</i> -C ₆ H ₄ Si(CH ₃) ₂ CH ₂ 	TaCl ₅ - <i>n</i> -Bu ₄ Sn	1900	163
Ph	C ₆ H ₄ , <i>m</i> -Ge(CH ₃) ₃	TaCl ₅ -9-BBN	> 100	164
Ph			1000	165

polyacetylenes containing functional groups. This section deals with the synthesis and properties of novel functional polyacetylenes.

3.11.4.1

Gas-Permeable Polyacetylenes

Application of substituted polyacetylenes as gas-permeable materials has been most intensively studied [166–170]. These studies are motivated by the extremely high gas permeability of poly(TMSP) [17, 171], which is the most permeable material among available polymers. Its oxygen permeability ($P_{O_2} = 4000\text{--}9000$ barrers) is about 10 times larger than that of poly(dimethylsiloxane). In addition to its high permeability, the ability of poly(TMSP) to give a free-standing film and its gas permeation mechanism, different from that of poly(dimethylsiloxane), have attracted much attention from membrane scientists.

Table 3.11-7 lists examples of the highly gas-permeable substituted polyacetylenes. The P_{O_2} values and oxygen/nitrogen selectivities (P_{O_2}/P_{N_2}) (25 °C) of about 80 substituted polyacetylenes have been measured so far [17]. Among those substituted polyacetylenes, many of the polymers with large P_{O_2} values contain spherical substituents, such as *t*-Bu, Me_3Si , and Me_3Ge groups. On the other hand, most of the less-permeable polyacetylenes possess long *n*-alkyl groups. When the

Tab. 3.11-7. Oxygen permeability coefficients (P_{O_2}) and P_{O_2}/P_{N_2} of highly permeable substituted polyacetylenes ($P_{O_2} > 400$ barrers).

$\begin{array}{c} \text{-(C=C)-} \\ \quad \\ R^1 \quad R^2 \end{array}$		P_{O_2} barrer ^a	P_{O_2}/P_{N_2}	Ref.
R^1	R^2			
CH ₃	SiMe ₃	$4 \times 10^3\text{--}9 \times 10^3$	1.8	17
CH ₃	SiEt ₃	860	2.0	172, 173
CH ₃	SiMe ₂ Et	500	2.2	173, 174, 175
CH ₃	SiMeEt ₂	440	2.1	173
CH ₃	SiMe ₂ - <i>i</i> -C ₃ H ₇	460	2.7	173, 174
CH ₃	GeMe ₃	7,800	–	154
CH ₃	<i>i</i> -C ₃ H ₇	2,700	2.0	176
C ₆ H ₅	C ₆ H ₅	6,000	1.3	177
C ₆ H ₅	C ₆ H ₄ - <i>p</i> -SiMe ₃	1,100–1,550	2.1	161, 162
C ₆ H ₅	C ₆ H ₄ - <i>m</i> -SiMe ₃	1,200	2.0	161, 162
C ₆ H ₅	C ₆ H ₄ - <i>m</i> -GeMe ₃	1,100	2.0	165
C ₆ H ₅	C ₆ H ₄ - <i>p</i> - <i>t</i> -C ₄ H ₉	1,100	2.2	156
2-naphthyl	C ₆ H ₅	4,300	1.6	178
2-naphthyl	C ₆ H ₄ - <i>p</i> -SiMe ₃	3,500	1.8	178
H	C ₆ H ₂ -2,4,5-(CF ₃) ₃	780	2.1	179
H	C ₆ H ₃ - <i>o</i> , <i>p</i> -(SiMe ₃) ₂	470	2.7	180
H	C ₆ H ₃ -2,5-(CF ₃) ₃	450	2.3	179

^a1 barrer = 1×10^{-10} cm³(STP) · cm/(cm² · s · cmHg).

phenyl group is the main substituent, the gas permeability of the resulting polyacetylenes is usually considerably lower. For comparison, the P_{O_2} values (P_{O_2}/P_{N_2}) of commercially available oxygen-permeable polymer membranes at 25 °C are as follows [167, 168, 181]: poly(dimethylsiloxane): 600 barrers (2.0); poly(4-methyl-1-pentene): 32 barrers; natural rubber: 23 barrers (2.3); and poly(oxy-2,6-dimethylphenylene): 15 barrers (5). Thus, compared to these commercial polymers, substituted polyacetylenes are very permeable to oxygen. The unusually high gas permeability of the polyacetylenes is attributed to the high free volume and unusual free volume distribution, which presumably derives from their low cohesive energy structure, stiff main chain, and spherical substituents.

Poly(diphenylacetylenes) with spherical ring substituents also exhibit large gas permeability [46, 156, 162, 165]. They are thermally very stable ($T_0 > 400$ °C) and possess film-forming ability. The ease of modifying ring substituents provides an opportunity to tune the permeability as well as the solubility and second-order conformation. The permeability of poly(diphenylacetylenes) significantly depends on the shape of ring substituents. Generally, those with bulky ring substituents, such as *t*-Bu, Me₃Si, and Me₃Ge groups, exhibit very large P_{O_2} values up to 1100–1200 barrers, which is about a quarter of that of poly(TMSP) and approximately twice as large as that of poly(dimethylsiloxane). Poly(phenylacetylenes) tend to show lower permeability than do poly(diphenylacetylenes).

Poly(diphenylacetylene) is insoluble in any solvent, whereas its derivatives with bulky ring-substituents are usually soluble in common solvents such as toluene and chloroform and give membranes by solution casting. Thus, a poly(diphenylacetylene) membrane has been prepared by the desilylation of a poly[1-phenyl-2-*p*-(trimethylsilyl)phenylacetylene] membrane catalyzed by trifluoroacetic acid [177]. The prepared polymer membrane shows high thermal stability, insolubility in any solvent, and very high gas permeability (e.g., an oxygen permeability of 6000 barrers at 25 °C), which is comparable to that of poly(TMSP). The high gas permeability of poly(diphenylacetylene) seems to be due to the generation of molecular-scale voids. In a similar way, poly[1- β -naphthyl-2-*p*-(trimethylsilyl)phenyl]acetylene] is soluble in common solvents, from whose membrane poly(1- β -naphthyl-2-phenylacetylene) membrane can be obtained by desilylation [178]. Both of the starting and desilylated polymers show large P_{O_2} values up to ca. 4000 barrers at 25 °C.

3.11.4.2

Optically Active Polyacetylenes

To date, many helical polymers have been synthesized. Helical-substituted polyacetylenes are expected to show unique properties and functions based on helicity and conjugation (e.g., the enantioselective permeable materials, polarization-sensitive electrooptical materials, asymmetric electrodes), and hence their synthesis is under intensive research.

4-(–)-Menthoxycarbonylphenylacetylene (**14**) was subjected to polymerization with several transition metal catalysts such as [(nbd)RhCl]₂ and WCl₆ [126]. The

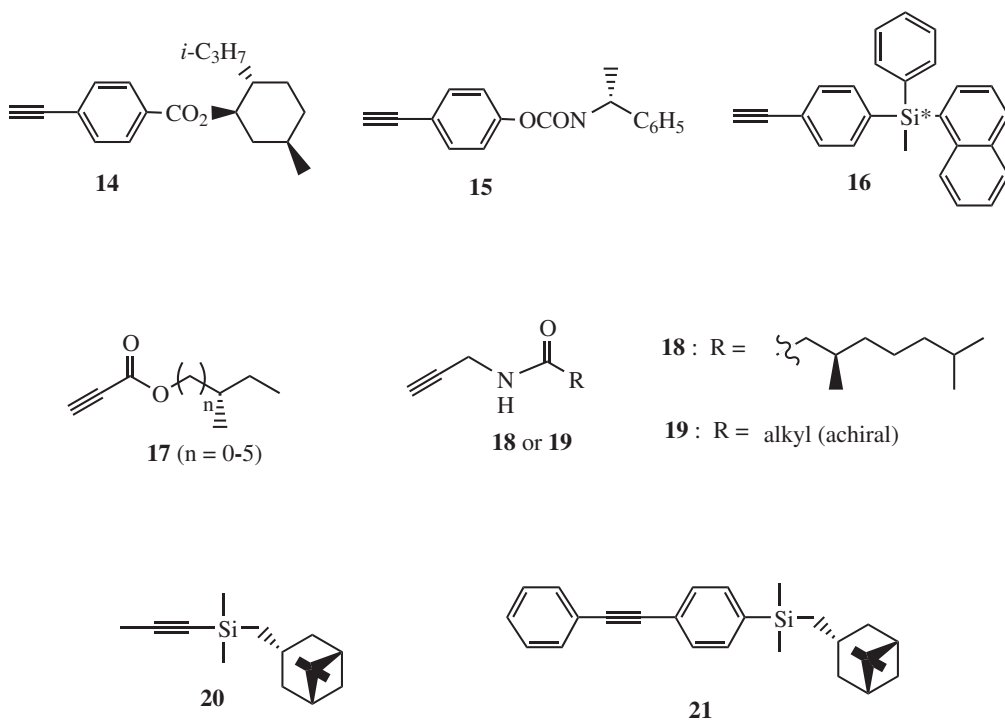


Fig. 3.11-5

resultant Rh-based polymer shows a large optical rotation and intense CD effects in the electric absorption region of the main chain. Thus, the polymer exists in a helical conformation with an excess of one-handed screw sense. The ability of the helical poly(phenylacetylene) to recognize chiral molecules has been demonstrated [127]. A stereoregular phenylacetylene-based polymer, poly(**15**), prepared with Rh catalyst has been shown to adopt a helical conformation. The nature of the helical conformation of poly(phenylacetylene) has been studied in detail [128]. It has been reported that poly(**16**) having bulky chiral silyl groups displays very intense CD effects [182].

Polymerization of propiolic esters having various chiral alkyl substituents, [**17**; $\text{HC}\equiv\text{CCO}_2\text{R}^*$, $\text{R}^* = (S)\text{-(CH}_2)_n\text{CHMeEt}$ ($n = 0\text{--}5$)] catalyzed by $[(\text{nbdt})\text{RhCl}]_2$ gives highly *cis* stereoregular polymers [66]. The stereoregular polymers with one to four alkylene spacers display intense CD effects and large optical rotations, indicating that they exist in helical conformations with an excess of a one-handed screw sense. The Mark-Houwink-Sakurada plots of the stereoregular (*cis*-transoidal) poly(propionic esters) clearly indicate the stiff main chain of poly(propionic esters); namely, the slope of the plot of poly(hexyl propionate) is 1.2, which is comparable to that of poly(hexyl isocyanate) [67]. The stiffness of poly(propionic esters) originates from the helical conformation with a large helical domain size. A clear cooperative effect of helical structure is observed in the chiral/achiral and the R/S copoly-

merizations, i.e., only a small amount of chiral substituents in the pendant groups leads to well-ordered helical poly(propionic esters) with an excess of one-handed screw sense [67].

A chiral monomer, (*R*)-*N*-propargyl-3,7-dimethyloctanamide (**18**) polymerizes with a Rh catalyst to give a polymer that has M_n of 8100 and 100% *cis* [71]. This polymer shows intense CD effects in the absorption region of the main-chain chromophore and a large optical rotation ($[\alpha]_D$) up to -1470° in chloroform, indicating that the polymer backbone is helical. The amide I absorption in the IR spectrum of this polymer appears at 1636 cm^{-1} irrespective of its concentration, shifting to a low wavenumber region compared to that of the monomer. These data lead to the conclusion that intramolecular hydrogen bonds are constructed between the pendant amide groups in poly(**18**). Achiral *N*-propargylalkylamides having various alkyl groups (**19a–g**; $\text{HC}\equiv\text{CCH}_2\text{NH}(\text{C}=\text{O})\text{R}$; R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *n*-C₅H₁₁, *n*-C₇H₁₅, respectively) have been homopolymerized or copolymerized with a chiral comonomer, **18**, in the presence of a Rh initiator [72]. Stable helical conformation, i.e., a long persistence length of the helical domain, is attainable for the polymer having β -branched alkyl chains (poly(**19e**), R = *i*-Bu), which is evidenced by a clear, positive, nonlinear relationship between the feed ratio of **19e** to **18** and the optical rotation of the copolymers. Poly(**19e-co-18**) (**19e/18** = 90/10 in feed) shows a strong CD signal in chloroform, whereas no CD effect is seen in a mixture of chloroform and methanol. This means that the helical conformation formed in chloroform is readily deformed into a random coil by addition of methanol.

The first example of chiral polymer from a disubstituted acetylene is a poly(TMSP)-based polymer, poly(**20**), which was synthesized in good yields using TaCl₅–Ph₃Bi [153]. Poly(**20**) displays small optical rotations, and its molar ellipticity of the Cotton effects is no more than a few hundred. The main chain of poly(**20**) is therefore not a well-ordered helix. This is probably due to the less-controlled geometrical structure (*cis* and *trans*) of the polymer backbone. Diphenylacetylene having a dimethyl(–)-pinanylsilyl group (**21**) was polymerized with Ta and Nb catalyst to give an extremely high-molecular-weight polymer in good yield [164]. The produced polymer exhibits a very large optical rotation ($[\alpha]_D > 2000^\circ$), and complicated but very intense CD effects appear in its absorption region. The desilylation of a poly(**21**) membrane provides a poly(diphenylacetylene) membrane, which exhibits a large specific rotation ($[\alpha]_D + 5590^\circ$) and intense CD signals in the 350–450 nm region, indicating that the main chain retains the helical conformation with a large excess of helix sense irrespective of the absence of any chiral pendant group [177].

3.11.4.3

Other Functional Polyacetylenes

Poly(1-alkynes) with phenylcyclohexyl mesogenic cores separated from the main chain by an alkylene spacer have been synthesized [108, 183]. These polymers prepared with Fe and Mo catalysts show a smectic A phase upon heating. Mo-

based polymers show higher transition temperatures compared to the Fe-based polymers. Novel photo-responsive liquid crystalline polyacetylenes [19, 20] that have azobenzenes as mesogens have also been prepared [109]. Thermally induced transitions from glassy to smectic and isotropic phases take place at 38 °C and 87 °C, respectively. This polymer undergoes reversible photochemical *trans*-to-*cis* and *cis*-to-*trans* isomerizations. Similarly, liquid crystalline polyacetylenes were synthesized by Mo- and W-based metathesis catalysts [110, 184]. These polymers possess 4'-cyano-4-biphenyloxy mesogenic centers and are mesomorphic, which was supported by the differential scanning calorimetry, polarizing optical microscopy, and XRD analyses. Liquid crystalline polyacetylenes bearing cholesteryl and other mesogenic groups have been synthesized by using a well-defined Schrock-type catalyst [111, 185]. Upon cooling, the cholesteryl-bearing polymer exhibits a mesophase of the smectic A type before undergoing a glass transition. Polyacetylenes containing 4-alkanyloxyphenyl *trans*-4-*n*-alkylcyclohexanoate were synthesized [186]. Polymers with alkylene spacers exhibited smectic phases and were photoluminescent.

Although the homopolymer of 9-anthrylacetylene obtained with W catalyst is insoluble [142], the polymer from 10-hexyloxycarbonyl-9-anthrylacetylene is a soluble, dark-purple polymer having an absorption maximum of 580 nm. This polymer exhibits the largest third-order nonlinear optical susceptibility among the polymers from monosubstituted acetylenes [187]. *N*-carbazoylacetylene also polymerizes with W catalysts, giving a polymer with high degree of main-chain conjugation and a large third-order susceptibility [145]. Photoconductivity of poly(phenylacetylenes) [123, 188] and disubstituted acetylene polymers [189] has been studied.

The luminescent property of conjugated polymers is one of the most important functions, and energetic study of the photo- and electroluminescence of substituted polyacetylenes has been made. Polymers that show intense luminescence are those from diphenylacetylenes and 1-phenyl-1-alkynes. Only weak red emissions are observed from monosubstituted arylacetylene polymers [190, 191]. A systematic investigation of the luminescence of poly(diphenylacetylenes) has found that these polymers exhibit photoluminescence around 530 nm and electroluminescence around 550 nm [192, 193]. In a similar way, poly(1-phenyl-1-alkynes) photochemically and electrochemically emit strong lights with spectral maxima located around 455 and 470 nm, respectively. Green and blue emissions are observed from the electroluminescent devices using poly(diphenylacetylenes) and poly(1-phenyl-1-alkynes), respectively, as the emission layers [191, 193–195]. Polymers from terminal acetylenes strongly luminesce upon photoexcitation [196]. Higher photoluminescent efficiency is observed for polyacetylenes having biphenyl moieties, which emit strong, deep-blue light (380 nm). This unexpected strong emission seems to originate from ordering of the pendant mesogens that enhance the main-chain conjugation of the polymers.

Poly(phenylacetylenes) having a stable radical in the *para*-substituent have been prepared by the direct polymerization of the radical-containing monomers [149–151]. Rh catalysts suit the polymerization of radical-containing monomers because

the radical groups do not interfere with Rh catalysts. Another type of radical-containing polymers is derived from the polymerization of the corresponding precursors followed by the oxidative polymer reaction [197–200]. Under appropriate conditions, polymers with very high spin concentration are available. Paramagnetic metalloporphyrins have been incorporated into poly(phenylacetylene) with the motivation of producing magnetically interacting polymers [201].

References

- 1 G. NATTA, G. MAZZANTI, AND P. CORRADINI, *Atti Accad. Naz. Lincei, Cl. Sci. Fis. Mat. Nat., Rend.*, 25, 3 (1958).
- 2 H. SHIRAKAWA, E. J. LOUIS, A. G. MACDIARMID, C. K. CHIANG, AND A. J. HEEGER, *J. Chem. Soc., Chem. Commun.*, 578 (1977).
- 3 H. SHIRAKAWA AND S. IKEDA, *Polym. J.*, 2, 231 (1971).
- 4 T. ITO, H. SHIRAKAWA, AND S. IKEDA, *J. Polym. Sci., Polym. Chem. Ed.*, 12, 11 (1974).
- 5 H. NAARMAN, *Synth. Met.*, 17, 223 (1987).
- 6 A. M. SAXMAN, R. LIEPENS, AND M. ALDISSI, *Prog. Polym. Sci.*, 11, 57 (1985).
- 7 J. C. W. CHIEN, *Polyacetylene*, Academic Press, New York, 1984.
- 8 T. A. SKOTHEIM (Ed.), *Handbook of Conducting Polymers*, Marcel Dekker, New York, 1986.
- 9 S. CURRAN, A. STAR-HAUSER, S. ROTH, in H. S. NALWA (Ed.), *Handbook of Organic Conductive Molecules and Polymers*, Vol. 2, Chapter 1, Wiley, Chichester, 1997.
- 10 T. MASUDA, K. HASEGAWA, AND T. HIGASHIMURA, *Macromolecules*, 7, 728 (1974).
- 11 T. MASUDA AND T. HIGASHIMURA, *Adv. Polym. Sci.*, 81, 121 (1986).
- 12 G. COSTA, in G. ALLEN (Ed.), *Comprehensive Polymer Science*, Vol. 4, Chapter 9, Pergamon Press, Oxford, 1989.
- 13 H. SHIRAKAWA, T. MASUDA, AND K. TAKEDA, in S. PATAI (Ed.), *The Chemistry of Triple-Bonded Functional Groups*, Supplement C2, Vol. 2, Chapter 17, Wiley, Chichester, 1994.
- 14 T. MASUDA, in J. C. SALAMONE (Ed.), *Polymeric Material Encyclopedia*, Vol. 1, p 32, CRC, 1996.
- 15 T. MASUDA, in S. KOBAYASHI (Ed.), *Catalysis in Precision Polymerization*, Chapter 2.4, Wiley, Chichester, 1997.
- 16 M. TABATA, T. SONE, AND Y. SADAHIRO, *Macromol. Chem. Phys.*, 200, 265 (1999).
- 17 K. NAGAI, T. MASUDA, T. NAKAGAWA, B. D. FREEMAN, AND I. PINNAU, *Prog. Polym. Sci.*, 26, 721 (2001).
- 18 R. NOMURA AND T. MASUDA, in J. I. KROSHWITZ (Ed.), *Encyclopedia of Polymer Science and Technology*, 3rd ed., Vol 1A, p1 (2003).
- 19 S.-K. CHOI, J. H. LEE, S. J. KANG, AND S. H. JIN, *Prog. Polym. Sci.* 22, 693 (1997).
- 20 S.-K. CHOI, Y.-S. GAL, S.-H. JIN, AND H. K. KIM, *Chem. Rev.* 100, 1645 (2000).
- 21 T. OGAWA, *Prog. Polym. Sci.*, 20, 943 (1995).
- 22 H. BALCAR AND M. PACOVSKA, *J. Mol. Catal. A*, 115, 101 (1997).
- 23 J. SEDLACEK, M. PACOVSKA, J. VOHLIDAL, Z. GRUBISIC-GALLOT, AND M. ZIGON, *Macromol. Chem. Phys.*, 196, 1705 (1995).
- 24 Y. NAKAYAMA, K. MASHIMA, AND A. NAKAMURA, *Macromolecules*, 26, 6267 (1993).
- 25 H. BALCAR AND J. SEDLACEK, *Macromol. Rapid Commun.*, 5, 771 (1994).
- 26 Y.-S. GAL, W.-C. LEE, S.-H. JIN, H.-J. LEE, S.-Y. KIM, D.-W. KIM, J.-M. KO, AND J.-H. CHUN, *J. Macromol. Sci., Pure Appl. Chem.* A38, 263 (2001).
- 27 N. MINAKI, S. HAYANO, AND T. MASUDA, *Polymer*, 43, 3579 (2002).
- 28 Y. TAMURA, Y. MISUMI, AND T. MASUDA, *Chem. Commun.*, 373 (1996).

- 29 Y. MISUMI, K. TAMURA, H. NAKAKO, AND T. MASUDA, *Polym. J.*, **30**, 581 (1998).
- 30 K. TAMURA, T. MASUDA, AND T. HIGASHIMURA, *Polym. Bull.*, **32**, 289 (1994).
- 31 K. TAMURA, T. MASUDA, AND T. HIGASHIMURA, *Polym. Bull.*, **30**, 537 (1993).
- 32 K. XU, H. PENG, J. W. Y. LAM, T. W. H. POON, Y. DONG, H. XU, Q. SUN, K. K. L. CHEUK, F. SALHI, P. P. S. LEE, AND B. Z. TANG, *Macromolecules*, **33**, 6918 (2000).
- 33 B. Z. TANG, K. XU, Q. SUN, P. P. S. LEE, H. PENG, X. WAN, T. W. H. POON, AND F. S. M. LEUNG, *ACS Symposium Series*, **760**, 146 (2000).
- 34 H. NAKAKO, Y. MISUMI, T. MASUDA, L. BENCZE, AND G. SZALAI, *Polym. J.*, **30**, 577 (1998).
- 35 T. SZYMANSKA-BUZAR AND I. CZELUSNIAK, *J. Mol. Catal. A*, **160**, 133 (2000).
- 36 T. J. KATZ AND S. J. LEE, *J. Am. Chem. Soc.*, **102**, 422 (1980).
- 37 D.-J. LIAW AND J.-S. TSAI, *J. Polym. Sci., Part A, Polym. Chem.*, **35**, 475 (1997).
- 38 D.-J. LIAW, H.-H. CHIANG, B.-H. JIN, AND E.-T. KANG, *Eur. Polym. J.*, **32**, 215 (1996).
- 39 R. R. SCHROCK, S. LUO, N. C. ZANETTI, AND H. H. FOX, *Organometallics*, **13**, 3396 (1994).
- 40 R. R. SCHROCK, S. LUO, J. C. LEE JR., N. C. ZANETTI, AND W. M. DAVIS, *J. Am. Chem. Soc.*, **118**, 3883 (1996).
- 41 H. H. FOX AND R. R. SCHROCK, *Organometallics*, **11**, 2763 (1992).
- 42 H. H. FOX, M. O. WOLF, R. O'DELL, B. L. LIN, R. R. SCHROCK, AND M. S. WRIGHTON, *J. Am. Chem. Soc.*, **116**, 2827 (1994).
- 43 F. J. SCHATTENMANN, R. R. SCHROCK, AND W. M. DAVIS, *J. Am. Chem. Soc.*, **118**, 3295 (1996).
- 44 S. KOLTZENBURG, E. EDER, F. STELZER, AND O. NUYKEN, *Macromolecules*, **32**, 21 (1999).
- 45 T. MASUDA AND H. TACHIMORI, *J. Macromol. Sci.-Pure Appl. Chem.*, **A31**, 1675 (1994).
- 46 T. MASUDA, M. TERAGUCHI, AND R. NOMURA, *ACS Symposium Series*, **733**, 28 (1999).
- 47 K. C. WALLACE, A. H. LIU, W. M. DAVIS, AND R. R. SCHROCK, *Organometallics*, **8**, 644 (1989).
- 48 R. NOMURA, H. NAKAKO, Y. FUKUSHIMA, AND T. MASUDA, *ACS Symposium Series*, **812**, 25 (2001).
- 49 Y. KISHIMOTO, M. ITO, T. MIYATAKE, T. IKARIYA, AND R. NOYORI, *Macromolecules*, **28**, 6662 (1995).
- 50 W. YANG, M. TABATA, S. KOBAYASHI, K. YOKOTA, AND A. SHIMIZU, *Polym. J.*, **23**, 1135 (1991).
- 51 M. TABATA, W. YANG, AND K. YOKOTA, *J. Polym. Sci., Part A, Polym. Chem.*, **32**, 1113 (1994).
- 52 K. KANKI, Y. MISUMI, AND T. MASUDA, *Macromolecules*, **32**, 2384 (1999).
- 53 Y. KISHIMOTO, P. ECKERLE, T. MIYATAKE, T. IKARIYA, AND R. NOYORI, *J. Am. Chem. Soc.*, **116**, 12131 (1994).
- 54 K. HIRAO, Y. ISHII, T. TERAOKA, Y. KISHIMOTO, T. MIYATAKE, T. IKARIYA, AND R. NOYORI, *Macromolecules*, **31**, 3405 (1998).
- 55 Y. KISHIMOTO, T. NOYORI, P. ECKERLE, T. MIYATAKE, AND T. IKARIYA, IN J. C. SALAMONE (Ed.), *Polymeric Material Encyclopedia*, Vol. 7, p 5051, CRC, Wiley, Chichester, 1996.
- 56 Y. KISHIMOTO, P. ECKERLE, T. MIYATAKE, M. KAINOSHO, A. ONO, T. IKARIYA, AND R. NOYORI, *J. Am. Chem. Soc.*, **121**, 12035 (1999).
- 57 Y. KISHIMOTO, T. MIYATAKE, T. IKARIYA, AND R. NOYORI, *Macromolecules*, **29**, 5054 (1996).
- 58 Y. MISUMI AND T. MASUDA, *Macromolecules*, **31**, 7572 (1998).
- 59 Y. MISUMI, K. KANKI, M. MIYAKE, AND T. MASUDA, *Macromol. Chem. Phys.*, **201**, 2239 (2000).
- 60 M. MIYAKE, Y. MISUMI, AND T. MASUDA, *Macromolecules*, **33**, 6636 (2000).
- 61 B. Z. TANG, W. H. POON, S. M. LEUNG, W. H. LEUNG, AND H. PENG, *Macromolecules*, **30**, 2209 (1997).
- 62 H. HORI, C. SIX, AND W. LEITNER, *Macromolecules*, **32**, 3178 (1999).
- 63 P. MASTRORILLI, C. F. NOBILE, V. GALLO, G. P. SURANNA, AND G.

- FARINOLA, J. *Mol. Catal. A*, **184**, 73 (2002).
- 64 E. YASHIMA, T. MATSUSHIMA, AND Y. OKAMOTO, *J. Am. Chem. Soc.*, **119**, 6345 (1997).
 - 65 M. TABATA, Y. INABA, K. YOKOTA, AND Y. NOZAKI, *J. Macromol. Sci.-Pure Appl. Chem. A*, **31**, 465 (1994).
 - 66 H. NAKAKO, R. NOMURA, M. TABATA, AND T. MASUDA, *Macromolecules*, **32**, 2861 (1999).
 - 67 H. NAKAKO, Y. MAYAHARA, R. NOMURA, M. TABATA, AND T. MASUDA, *Macromolecules*, **33**, 3978 (2000).
 - 68 R. NOMURA, Y. FUKUSHIMA, H. NAKAKO, AND T. MASUDA, *J. Am. Chem. Soc.*, **122**, 8830 (2000).
 - 69 M. L. SAITO, K. MAEDA, H. ONOUCHI, AND E. YASHIMA, *Macromolecules*, **33**, 4616 (2000).
 - 70 K. MAEDA, H. GOTO, AND E. YASHIMA, *Macromolecules*, **34**, 1160 (2001).
 - 71 R. NOMURA, J. TABEI, AND T. MASUDA, *J. Am. Chem. Soc.*, **123**, 8430 (2001).
 - 72 R. NOMURA, J. TABEI, AND T. MASUDA, *Macromolecules*, **35**, 2955 (2002).
 - 73 K. YAMADA, R. NOMURA, AND T. MASUDA, *Macromolecules*, **33**, 9179 (2000).
 - 74 M. V. RUSSO, G. IUCCI, A. FURLANI, AND G. POLZONETTI, *Polymer*, **36**, 4867 (1995).
 - 75 M. V. RUSSO, A. FURLANI, M. CUCCU, AND G. POLZONETTI, *Polymer*, **37**, 1715 (1995).
 - 76 H. BALCAR, P. HOLLER, J. SEDLACEK, AND V. BLECHTA, *Collect. Czech. Chem. Commun.*, **63**, 1803 (1998).
 - 77 C. B. GORMAN, R. W. VEST, T. U. PALOVICH, AND S. SERRON, *Macromolecules*, **32**, 4157 (1999).
 - 78 K. TSUCHIHARA, *Polymer*, **41**, 2691 (2000).
 - 79 W. E. DOUGLAS, *Appl. Organometal. Chem.*, **15**, 23 (2001).
 - 80 T. MASUDA, T. YOSHIMURA, J. FUJIMORI, AND T. HIGASHIMURA, *J. Chem. Soc., Chem. Commun.*, 1805 (1987).
 - 81 T. MASUDA, T. YOSHIMURA, AND T. HIGASHIMURA, *Macromolecules*, **22**, 3804 (1989).
 - 82 T. MASUDA, K. MISHIMA, J. FUJIMORI, M. NISHIDA, AND T. HIGASHIMURA, *Macromolecules*, **25**, 1401 (1992).
 - 83 T. MASUDA, T. FUJIMORI, Z. A. R. MOHAMAD, AND T. HIGASHIMURA, *Polym. J.*, **25**, 535 (1993).
 - 84 T. MIZUMOTO, T. MASUDA, AND T. HIGASHIMURA, *Macromol. Chem. Phys.*, **196**, 1769 (1995).
 - 85 T. MASUDA, K. MISHIMA, H. SEKI, M. NISHIDA, AND T. HIGASHIMURA, *Polym. Bull.*, **32**, 19 (1994).
 - 86 M. NAKANO, T. MASUDA, AND T. HIGASHIMURA, *Macromolecules*, **27**, 1344 (1994).
 - 87 H. KANESHIRO, T. MASUDA, AND T. HIGASHIMURA, *Polym. Bull.*, **35**, 17 (1995).
 - 88 H. KUBO, S. HAYANO, AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **38**, 2697 (2000).
 - 89 S. HAYANO, T. MASUDA, *J. Macromol. Sci., Pure Appl. Chem.*, **A37**, 853 (2000).
 - 90 H. KUBO, S. HAYANO, Y. MISUMI, AND T. MASUDA, *Macromol. Chem. Phys.*, **203**, 279 (2002).
 - 91 T. MASUDA, H. IZUMIKAWA, Y. MISUMI, AND T. HIGASHIMURA, *Macromolecules*, **29**, 1167 (1996).
 - 92 S. HAYANO, T. ITOH, AND T. MASUDA, *Polymer*, **40**, 4071 (1999).
 - 93 H. KANESHIRO, S. HAYANO, AND T. MASUDA, *Polym. J.*, **31**, 348 (1999).
 - 94 T. MASUDA, H. KANESHIRO, S. HAYANO, Y. MISUMI, AND L. BENCZE, *J. Macromol. Sci.-Pure Appl. Chem.*, **A34**, 1977-1995 (1997).
 - 95 S. HAYANO AND T. MASUDA, *Macromol. Chem. Phys.*, **198**, 3041 (1997).
 - 96 S. HAYANO AND T. MASUDA, *Macromolecules*, **31**, 3170 (1998).
 - 97 T. MASUDA, S. HAYANO, E. IWAWAKI, AND R. NOMURA, *J. Mol. Catal.*, **133**, 213 (1998).
 - 98 S. HAYANO AND T. MASUDA, *Macromolecules*, **32**, 7344 (1999).
 - 99 S. HAYANO AND T. MASUDA, *Macromol. Chem. Phys.*, **201**, 233 (2000).
 - 100 E. IWAWAKI, S. HAYANO, AND T. MASUDA, *Polymer*, **41**, 4429 (2000).
 - 101 E. IWAWAKI, S. HAYANO, AND T. MASUDA, *Polymer*, **42**, 4055 (2001).
 - 102 M. BUCHMEISER AND R. R. SCHROCK, *Macromolecules*, **28**, 6642 (1995).
 - 103 M. R. BUCHMEISER, N. SCHULER, G. KALTENHAUSER, K.-H. ONGANIA,

- I. LAGOJA, K. WURST, AND H. SCHOTTENBERGER, *Macromolecules*, **31**, 3175 (1998).
- 104 M. R. BUCHMEISER, *Macromolecules*, **30**, 2274 (1997).
- 105 K. KANKI, Y. MISUMI, AND T. MASUDA, *Inorg. Chim. Acta*, **336**, 101 (2002).
- 106 B. OCHIAI, I. TOMITA, T. ENDO, *Macromol. Rapid Commun.*, **22**, 1485 (2001).
- 107 H. BALCAR, T. KALISZ, J. SEDLACEK, V. BLECHTA, AND P. MATEJKA, *Polymer*, **39**, 4443 (1998).
- 108 S. OH, R. EZAKI, K. AKAGI, AND H. SHIRAKAWA, *J. Polym. Sci., Part A, Polym. Chem.*, **31**, 2977 (1993).
- 109 H. GOTO, K. AKAGI, AND H. SHIRAKAWA, *Synth. Met.* **84**, 373 (1997).
- 110 B. Z. TANG, X. KONG, X. WAN, H. PENG, W. Y. LAM, X. D. FENG, AND H. S. KWOK, *Macromolecules*, **31**, 2419 (1998).
- 111 S. KOLTZENBURG, F. STELZER, AND O. NUYKEN, *Macromol. Chem. Phys.*, **200**, 821 (1999).
- 112 M. MITSUYAMA, K. KONDO, *Macromol. Chem. Phys.*, **201**, 1613 (2000).
- 113 YAMAGUCHI, K. OSAKADA, AND T. YAMAMOTO, *Inorg. Chim. Acta*, **220**, 35 (1994).
- 114 M. V. RUSSO, A. FURLANI, P. ALTAMURA, I. FRATODDI, AND G. POLZONETTI, *Polymer*, **38**, 3677 (1997).
- 115 M. MITSUYAMA, R. ISHII, K. KONDO, *J. Polym. Sci. Part A. Polym. Chem.*, **38**, 3419 (2000).
- 116 T. SATA, R. NOMURA, AND T. MASUDA, *Polym. Bull.*, **41**, 395 (1998).
- 117 Y.-S. GAL, B. JUNG, W.-C. LEE, H.-J. LEE, AND S.-K. CHOI, *Macromolecules*, **28**, 2086 (1995).
- 118 Y.-S. GAL, *Eur. Polym. J.*, **33**, 169 (1997).
- 119 Y. FUJITA, Y. MISUMI, M. TABATA, AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **36**, 3157 (1998).
- 120 T. YOSHIDA, Y. ABE, K. T. MASUDA, T. HIGASHIMURA, *J. Polym. Sci., Part A, Polym. Chem.*, **34**, 2229 (1996).
- 121 M. V. RUSSO, A. FURLANI, AND R. D'AMATO, *J. Polym. Sci., Part A, Polym. Chem.*, **36**, 93 (1998).
- 122 S. M. A. KARIM, R. NOMURA, AND T. MASUDA, *Polym. Bull.*, **43**, 305 (1999).
- 123 VOHLÍDAL, J. SEDLÁČEK, M. PACOVSKÁ, O. LAVASTRE, P. H. DIXNEUF, H. BALCAR, AND J. PFLEGER, *Polymer*, **38**, 3359 (1997).
- 124 B. Z. TANG, X. KONG, X. WAN, AND X. D. FENG, *Macromolecules*, **30**, 5620 (1998).
- 125 X. KONG, J. W. Y. LAM, AND B. Z. TANG, *Macromolecules*, **32**, 1722 (1999).
- 126 T. AOKI, M. KOKAI, K. SHINOHARA, AND E. OIKAWA, *Chem. Lett.*, 2009 (1993).
- 127 E. YASHIMA, S. HUANG, AND Y. OKAMOTO, *J. Chem. Soc., Chem. Commun.*, 1811 (1994).
- 128 E. YASHIMA, S. HUANG, T. MATSUSHIMA, AND Y. OKAMOTO, *Macromolecules*, **28**, 4184 (1995).
- 129 E. YASHIMA, Y. MAEDA, AND Y. OKAMOTO, *J. Am. Chem. Soc.*, **120**, 8895 (1998).
- 130 T. SUGIMOTO, T. KOREMOTO, T. INOUE, R. NOMURA, AND T. MASUDA, *Polym. Bull.*, **42**, 55 (1999).
- 131 E. YASHIMA, Y. MAEDA, T. MATSUSHIMA, AND Y. OKAMOTO, *Chirality*, **9**, 593 (1997).
- 132 TSUCHIHARA, T. MASUDA, T. HIGASHIMURA, M. NISHIDA, AND H. MURAMATSU, *Polym. Bull.*, **23**, 505 (1990).
- 133 T. MASUDA, T. HAMANO, K. TSUCHIHARA, AND T. MASUDA, *Macromolecules*, **23**, 1374 (1990).
- 134 T. MIZUMOTO, T. MASUDA, T. HIGASHIMURA, *J. Polym. Sci., Part A, Polym. Chem.*, **31**, 2555 (1993).
- 135 O. LAVASTRE, S. CABIOCH, P. H. DEXNEUF, J. SEDLACEK, AND J. VOHLÍDAL, *Macromolecules*, **32**, 4477 (1999).
- 136 J. VOHLÍDAL, J. SEDLACEK, N. PATEV, O. LAVASTRE, P. H. DIXNEUF, S. CABIOCH, H. BALCAR, J. PFLEGER, AND V. BLECHTA, *Macromolecules*, **32**, 6439 (1999).
- 137 T. YOSHIMURA, T. MASUDA, T. HIGASHIMURA, K. OKUHARA, AND T. UEDA, *Macromolecules*, **24**, 6053 (1991).
- 138 TERAGUCHI AND T. MASUDA, *Macromolecules*, **33**, 240 (2000).
- 139 H. BALCAR, J. SEDLACEK, J. VOHLÍDAL,

- J. ZEDNLIK, AND V. BLECHTA, *Macromol. Chem. Phys.*, **200**, 2591 (1999).
- 140 H. BALCAR, J. SEDLACEK, J. ZEDNIK, V. BLECHTA, P. KUBAT, AND J. VOHLIDAL, *Polymer*, **42**, 6709 (2001).
 - 141 J. SEDLACEK, J. VOHLIDAL, N. PATEV, M. PACOVSKA, S. CABIOCH, O. LAVASTRE, P. H. DIXNEUF, H. BALCAR, P. MATEJKA, *Macromol. Chem. Phys.*, **200**, 972 (1999).
 - 142 K. NANJO, S. M. A. KARIM, R. NOMURA, T. WADA, H. SASABE, AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **37**, 277 (1999).
 - 143 K. MUSIKABHUMMA AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **36**, 3131 (1998).
 - 144 S. M. A. KARIM, K. MUSIKABHUMMA, R. NOMURA, AND T. MASUDA, *Proc. Jpn. Acad. Ser. B*, **75**, 97 (1999).
 - 145 T. SATA, R. NOMURA, T. WADA, H. SASABE, AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **36**, 2489 (1998).
 - 146 T. KAKUCHI, S. MATSUNAMI, H. KAMIMURA, F. ISHII, T. UESAKA, AND K. YOKOTA, *J. Polym. Sci., Part A, Polym. Chem.*, **33**, 1431 (1998).
 - 147 T. KANEKO, T. HORIE, M. ASANO, T. AOKI, AND E. OIKAWA, *Macromolecules*, **30**, 3118 (1997).
 - 148 T. SHIMIZU AND T. YAMAMOTO, *Chem. Commun.*, 515 (1999).
 - 149 DULOG AND S. LUTZ, *Makromol. Chem., Rapid Commun.*, **14**, 147 (1993).
 - 150 Y. MIURA, M. MATSUMOTO, AND Y. USHITANI, *Macromolecules*, **26**, 2628 (1993).
 - 151 A. FUJII, T. ISHIDA, N. KOGA, AND H. IWAMURA, *Macromolecules*, **24**, 1077 (1991).
 - 152 T. MASUDA, T. MATSUMOTO, T. YOSHIMURA, AND T. HIGASHIMURA, *Macromolecules*, **23**, 4902 (1990).
 - 153 T. AOKI, K. SHINOHARA, T. KANEKO, AND E. OIKAWA, *Macromolecules*, **29**, 4192 (1996).
 - 154 G. KWAK AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **38**, 2964 (2000).
 - 155 TERAGUCHI AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **37**, 4546 (1999).
 - 156 H. KOUZAI, T. MASUDA, AND T. HIGASHIMURA, *J. Polym. Sci., Part A, Polym. Chem.*, **32**, 2523 (1994).
 - 157 H. KOUZAI, T. MASUDA, AND T. HIGASHIMURA, *Polymer*, **35**, 4920 (1994).
 - 158 H. TACHIMORI, T. MASUDA, H. KOUZAI, AND T. HIGASHIMURA, *Polym. Bull.*, **32**, 133 (1994).
 - 159 T. YOSHIMURA AND M. ASANO, *Polym. J.*, **26**, 159 (1994).
 - 160 H. TACHIMORI AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **33**, 2079 (1995).
 - 161 K. TSUCHIHARA, T. MASUDA, AND T. HIGASHIMURA, *J. Am. Chem. Soc.*, **113**, 8548 (1991).
 - 162 K. TSUCHIHARA, T. MASUDA, AND T. HIGASHIMURA, *Macromolecules*, **25**, 8516 (1992).
 - 163 M. TERAGUCHI AND T. MASUDA, *J. Polym. Sci., Part A, Polym. Chem.*, **36**, 2721 (1998).
 - 164 T. AOKI, Y. KOBAYASHI, T. KANEKO, E. OIKAWA, Y. YAMAMURA, Y. FUJITA, M. TERAGUCHI, R. NOMURA, AND T. MASUDA, *Macromolecules*, **32**, 79 (1999).
 - 165 H. ITO, T. MASUDA, AND T. HIGASHIMURA, *J. Polym. Sci., Part A, Polym. Chem.*, **34**, 2925 (1996).
 - 166 D. S. BRESLOW, *Prog. Polym. Sci.*, **18**, 1141 (1993).
 - 167 S. A. STERN, *J. Membr. Sci.*, **94**, 1 (1994).
 - 168 R. E. KESTING AND A. K. FRITZSCHE, *Polymeric Gas Separation Membranes*, Wiley, New York, 1993.
 - 169 H. ODANI AND T. MASUDA, in N. TOSHIMA (Ed.), *Polymers for Gas Separation*, Chapter 4, VCH, New York, 1992.
 - 170 B. D. FREEMAN AND I. PINAU (Eds.), *ACS Symposium Series*, **733** (1999).
 - 171 T. MASUDA, E. ISOBE, T. HIGASHIMURA, AND K. TAKADA, *J. Am. Chem. Soc.*, **105**, 7473 (1983).
 - 172 T. MASUDA, E. ISOBE, T. HAMANO, AND T. HIGASHIMURA, *J. Polym. Sci., Part A, Polym. Chem.*, **25**, 1353 (1987).
 - 173 L. M. ROBESON, W. F. BURGOYNE, M. LANGSAM, A. C. SAVOCA, AND C. F. TIEN, *Polymer*, **35**, 4970 (1994).
 - 174 A. C. SAVOCA, A. D. SURNAMER, AND

- C. F. TIEN, *Macromolecules*, 26, 6211 (1993).
- 175 K. TAKADA, H. MATSUYA, T. MASUDA, AND T. HIGASHIMURA, *J. Appl. Polym. Sci.*, 30, 1605 (1985).
- 176 A. MORISATO AND I. PINNAU, *J. Membr. Sci.*, 121, 243 (1996).
- 177 M. TERAGUCHI AND T. MASUDA, *Macromolecules*, 35, 1149 (2002).
- 178 T. SAKAGUCHI, G. KWAK, AND T. MASUDA, *Polymer*, 43, 3937 (2002).
- 179 Y. HAYAKAWA, M. NISHIDA, T. AOKI, AND H. MURAMATSU, *J. Polym. Sci., Part A., Polym. Chem.*, 30, 873 (1992).
- 180 T. AOKI, H. NAKAHARA, Y. HAYAKAWA, M. KOKAI, AND E. OIKAWA, *J. Polym. Sci., Part A., Polym. Chem.*, 32, 849 (1994).
- 181 S. PAULY, in J. BRANDRUP, E. H. IMMERGUT, E. A. GRULKE (Eds.), *Polymer Handbook*, 4th ed, New York: Wiley, 1999, VI/543.
- 182 G. KWAK AND T. MASUDA, *Macromolecules*, 33, 6633 (2000).
- 183 S.-Y. OH, K. AKAGI, H. SHIRAKAWA, AND K. ARAYA, *Macromolecules*, 26, 6203 (1993).
- 184 W. Y. LAM, Y. DONG, K. L. CHEUK, J. LUO, Z. XIE, H. S. KWOK, Z. MO, AND B. Z. TANG, *Macromolecules*, 35, 1229 (2002).
- 185 S. KOLTZENBURG, D. WOLFF, F. STELZER, J. SPRINGER, AND O. NUYKEN, *Macromolecules*, 31, 9166 (1998).
- 186 C.-H. TING, J.-T. CHEN, AND C.-S. HSU, *Macromolecules*, 35, 1180 (2002).
- 187 R. NOMURA, S. M. A. KARIM, H. KAJII, R. HIDAYAT, K. YOSHINO, AND T. MASUDA, *Macromolecules*, 33, 4313 (2000).
- 188 J. SEDLACEK, J. VOHLIDAL, S. CABIOCH, O. LAVASTRE, P. DIXNEUF, H. BALCAR, M. STICHA, J. PFLEGER, AND V. BLECHTA, *Macromol. Chem. Phys.*, 199, 155 (1998).
- 189 S. C. SUH, S. C. SHIM, H.-W. SHIN, AND Y.-R. KIM, *Macromol. Chem. Phys.*, 202, 14 (2001).
- 190 R. HIDAYAT, M. HIROHATA, A. FUJII, M. TERAGUCHI, T. MASUDA, AND K. YOSHINO, *Jpn. J. Appl. Phys.*, 38, 931 (1999).
- 191 R. SUN, T. MASUDA, AND T. KOBAYASHI, *Synth. Met.*, 91, 301 (1997).
- 192 K. TADA, R. HIDAYAT, M. HIROHATA, M. TERAGUCHI, T. MASUDA, AND K. YOSHINO, *Jpn. J. Appl. Phys.*, 35, L1138 (1996).
- 193 R. SUN, T. MASUDA, AND T. KOBAYASHI, *Jpn. J. Appl. Phys.*, 35, L1673 (1996).
- 194 R. HIDAYAT, M. HIROHATA, K. TADA, M. TERAGUCHI, T. MASUDA, AND K. YOSHINO, *Jpn. J. Appl. Phys.*, 36, 3740 (1997).
- 195 M. HIROHATA, K. TADA, R. HIDAYAT, T. MASUDA, AND K. YOSHINO, *Jpn. J. Appl. Phys.*, 36, L302 (1997).
- 196 Y. M. HUANG, J. W. Y. LAM, K. K. L. CHEUK, W. GE, AND B. Z. TANG, *Macromolecules*, 32, 5976 (1999).
- 197 YOSHIOKA, H. NISHIDE, T. KANEKO, H. YOSHIKI, AND E. TSUCHIDA, *Macromolecules*, 25, 3838 (1992).
- 198 H. NISHIDE, T. KANEKO, N. YOSHIOKA, H. AKIYAMA, M. IGARASHI, AND E. TSUCHIDA, *Macromolecules*, 26, 4567 (1993).
- 199 L. DULOG AND P. BOGNAR, *Macromol. Rapid Commun.*, 16, 43 (1995).
- 200 Y. MIURA, K. INUI, F. YAMAGUCHI, M. INOUE, Y. TEKI, T. TAKUI, AND K. ITOH, *J. Polym. Sci., Part A, Polym. Chem.*, 30, 959 (1992).
- 201 K. ARAMATA, A. KAJIWARA, AND M. KAMACHI, *Macromolecules*, 28, 4774 (1995).

3.12

Commercial Applications of Ruthenium Olefin Metathesis Catalysts in Polymer Synthesis

Mark S. Trimmer

3.12.1

Introduction

Previous chapters have demonstrated that olefin metathesis technology has broad applicability for polymer synthesis. In general, there are two major classifications of metathesis polymerization chemistry: ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) polymerization. Historically, ROMP has achieved a degree of commercial success due to the ready availability of bulk quantities of several cyclic olefin monomers from petrochemical refining, while ADMET has largely been an academic curiosity. However, with the current emphasis on nanoengineered materials and the functional group tolerance and degree of process control afforded by the current generation of ruthenium olefin metathesis catalysts, it is believed that both of these technologies will find increasing commercial opportunities.



3.12.2

Background

Olefin metathesis chemistry began to achieve significant commercial interest during the 1960s, primarily for redistribution of petrochemical feedstocks via cross-metathesis with heterogeneous catalysts. The first example was the Phillips triolefin process that converted then less-useful propylene into a more desirable mixture of ethylene and 2-butene. Interestingly, the situation was reversed in

the 1970s when Lyondell began to use a similar process to convert ethylene and 2-butene to high-grade propylene, which had then become much more commercially attractive. Other significant examples are processes for neohexene, isoamylene, and various α,ω -diolefins and the Shell Higher Olefins Process (SHOP) for detergent-grade internal olefins.

After establishing roots in petrochemical processing, ring-opening metathesis polymerization of hydrocarbon feedstocks such as cyclopentene (polypentenamer), cyclooctene (e.g., Vestenamer®) [1], norbornene (e.g., Norsorex®) [2], and dicyclopentadiene (e.g., Metton®, Telene®, and Pentam™) [3] became the next significant commercial application of olefin metathesis processes. As with petrochemical processing, these have typically been produced using ill-defined heterogeneous catalyst systems based on molybdenum, tungsten, or ruthenium salts along with various co-catalysts and/or promoters and inhibitors. For example, norbornene is polymerized using RuCl_3/HCl in butanol. Metathesis-polymerized polycycloalkenes tend to be elastomeric materials, making them good shock insulators and viscoelastic layer dampers. Because metathesis preserves the double bonds, they are also vulcanizable. Vestenamer® is one of the more commercially successful of these materials and is most commonly used as a co-vulcanizable processing aid in the rubber industry. Norsorex® is commonly utilized in the automotive industry for vibration and noise dampening and for soft seals and gaskets. In addition, Norsorex® can absorb 5–10 times its mass of oil, making it useful for oil-spill recovery.

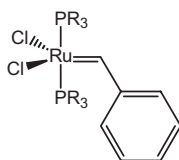
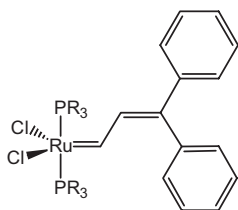
During the 1980s, a significant commercial target was resins based on ROMP of dicyclopentadiene (DCPD), an inexpensive byproduct of the petrochemical industry. In contrast to the polycycloalkenes described above, polydicyclopentadiene (poly-DCPD) undergoes significant cross-linking through the secondary double bond and forms a more traditional “rigid” thermoset material. The primary interest has been in direct reaction injection molding (RIM) of parts with high toughness and corrosion resistance. The three major DCPD product lines (Metton®, Telene®, and Pentam™) have achieved limited success (probably somewhat less than \$50 million in global annual sales) in applications such as golf cart bumpers, snowmobile and truck fascia, chemical process components, and industrial parts. As with the other polymers, the synthetic utility and commercial viability of these systems have been mitigated by the high air and moisture sensitivity of the traditional ill-defined catalyst systems.

3.12.3 New Developments

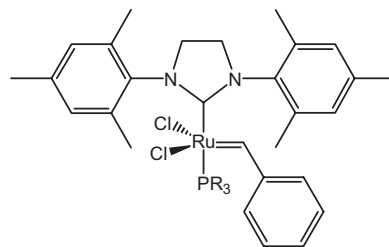
Virtually all current commercial metathesis polymerization processes utilize the traditional ill-defined catalyst systems. The reasons for this include the extreme cost sensitivity inherent in the commodity material business and the relative novelty of the new systems. Even though the so-called Grubbs and Schrock catalysts

were developed through focused research programs going back to the 1970s, the first truly promising catalysts did not become widely known and available until the mid-1990s. Although the Schrock catalysts typically show higher reactivity, which is very important for materials applications, they retain the air and moisture sensitivity, and much of the functional group intolerance, of the traditional ill-defined catalyst systems while carrying a premium price tag. The first generation of Grubbs catalysts demonstrated attractive functional group tolerance and handling characteristics but lacked the reactivity needed by the materials industry.

Grubbs first reported a well-defined ruthenium carbene catalyst in 1992 [4, 5]. Although these complexes did catalyze ROMP, they were difficult and expensive to prepare, and their activity was orders of magnitude lower than the traditional or Schrock catalysts, making them impractical for commercial polymer applications. After further refinement, Grubbs reported the catalyst $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHC}_6\text{H}_5$ (Cy = cyclohexyl), which is now widely known as the “Grubbs catalyst,” in 1996 [6, 7]. This catalyst proved to be much easier to prepare and exhibited improved reactivity but was still not efficient enough for many polymer applications. Finally, in 1999, Grubbs and others introduced even better ruthenium catalysts that incorporated *N*-heterocyclic carbene ligands in place of one of the phosphine ligands [8–10]. The so-called second-generation Grubbs catalysts [11] exhibit reactivities and turnover numbers competitive with traditional metathesis catalysts while still offering functional group tolerance and ease of handling.



Grubbs Catalyst

Second-Generation
Grubbs Catalyst

3.12.4 Poly-DCPD

Although the new generations of well-defined catalysts such as those developed by Grubbs and Schrock are just beginning to be adopted in industry, their first inroads were made in the area of poly-DCPD. Advanced Polymer Technologies (APT) was the first company to recognize the importance of the user-friendly features offered by the Grubbs catalysts, taking a license to the technology in the early 1990s. In 2000, APT formed a joint venture with BF Goodrich, the developer of

the Telene® family of poly-DCPD resins, to combine the old and new catalyst technologies under one roof. This joint venture took on the name Cymetech, LLC and is headquartered in Huntsville, Texas [12]. After the spin-off of the BF Goodrich Performance Materials division, the resulting Noveon's share of the joint venture was ultimately transferred to Sterling JA, LLC, a privately held investment firm. Along with its Ultrane® DCPD and Telene® poly-DCPD product lines acquired from Goodrich, Cymetech has also recently launched its Prometa® line of "engineering" poly-DCPD resins based on the Grubbs catalyst technology.

Although Cymetech has largely focused on RIM components and corrosion applications, mainstays of the traditional poly-DCPD materials, it has promoted other applications through licensing. For example, A. O. Smith Corporation launched a line of high-performance, corrosion-resistant composite piping, trademarked Cyonyx®, in the late 1990s. Compared with traditional steel or composite piping products, Cyonyx® offered low-weight, phenomenal impact resistance and unsurpassed resistance to halogens. In creating Cyonyx®, Smith developed novel composite technology [13] and demonstrated flame-retarding methodologies [14]. Unfortunately, shortly after the spin-off and merger of A. O. Smith's fiberglass piping division to form Smith Fibercast, this promising, but not yet established, product was discontinued.

In Asia, Cymetech formed a significant partnership with Hitachi Chemical, which has promoted the technology under its Metathene™ designation. Hitachi is developing and licensing Metathene™ for a variety of electronic [15] and consumer (e.g., bathroom fixtures) applications. In the United States, Cymetech has co-developed several areas of poly-DCPD product technology in conjunction with Materia, Inc. [16], a small company based in Pasadena, California, that is promoting the commercialization of various catalyst technologies, including olefin metathesis by well-defined catalysts. For example, in the polymer area, Materia has patented technology related to variable-density composites [17] (including syntactic foam and metal-filled tooling and prototyping materials) and for methods for adhering hydrocarbon resins such as poly-DCPD to various surfaces [18]. Materia has also demonstrated the infusion of very low-viscosity cycloolefin resins into porous substrates, such as wood, to make novel composite materials with enhanced mechanical performance, improved chemical and moisture resistance, and greater durability [19].

Based on the unique combination of properties offered by the poly-DCPD material, including ready processability combined with exceptional toughness and corrosion resistance, Materia has also been evaluating a variety of other applications including ballistics and blast containment, electronics and optoelectronics, coatings, microreplication/microfabrication, and high-performance composites and nanocomposites. Materia has also licensed poly-DCPD technology to Easton Sports, a manufacturer of sports equipment based in Van Nuys, California, and helped them to develop several product lines, including goods for baseball, hockey, and archery. The first Easton products manufactured using poly-DCPD technology were launched in mid-2003.



Fig. 3.12-1. A poly-DCPD casting (1.5 inches thick) polymerized with ruthenium technology is impenetrable to 9-mm bullets.

3.12.5

Other ROMP Polymers

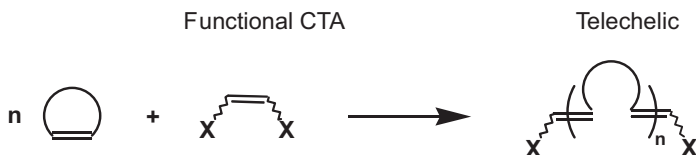
The robustness and high activity of the ruthenium-based metathesis catalysts enable surprising new applications of ROMP technology. An excellent case in point is the contact metathesis polymerization (CMP) technology developed at Lord Corporation [20]. In this process, a substrate surface (e.g., a metal component) is first treated with olefin metathesis catalyst. This substrate can then be bonded to an appropriate rubber or plastic via an intervening layer of a metathesis-polymerizable resin such as DCPD or ethylenenorbornene (ENB). The method is reported to yield excellent bonding between the substrate and the rubber/plastic material. Lord has also demonstrated that this process has utility for coating fibers [21] and other substrates [22].

ROMP polymers, including poly-DCPD, are also proving to be polymers of choice as healing agents in the new field of self-healing polymers and composites. Researchers at the University of Illinois have demonstrated this technology largely by making use of microencapsulated DCPD and the versatile Grubbs catalyst [23, 24]. In these systems, the encapsulated liquid resin (DCPD) is released upon damage to the composite, comes in contact with living catalyst dispersed throughout the matrix, and polymerizes to heal the composite. Although this field is still very young, companies have already begun seriously evaluating this new materials concept. For example, researchers at the Acushnet Company (holder of the Titleist®, Cobra®, Pinnacle®, and Footjoy® brand names that will be well known to those readers who are golfers) have already filed patent applications regarding the use of this technology in golf ball [25] and other sporting goods applications [26].

Several other corporate groups have taken advantage of the functional group tolerance of the ruthenium-based carbene catalysts to explore other ROMP poly-

mers derived from functionalized cyclic olefins. Ciba has patented several ROMP methods and compositions involving well-defined catalyst systems [27], although none of these appear to have been commercialized yet. Researchers at Eastman Chemical have patented norbornene copolymers [28, 29] based on functionalized norbornene monomers derivable from Eastman's EpB[®] oxirane (3,4-epoxy-1-butene) and related derivatives. Under an Advanced Technology Program (ATP) project with the California Institute of Technology (Caltech) and other collaborators [30], Cryovac has developed new regioregular-functionalized hydrocarbon polymers with interesting barrier properties via ROMP of 5-cyclooctene-*trans*-1,2-diol and related monomers [31, 32]. In the Cryovac case, the high degree of regiocontrol offered by olefin metathesis enables the preparation of the specific polymer structures required for low oxygen permeability.

Metathesis polymerization in the presence of chain-transfer agents (CTAs) has been demonstrated to be an ideal way to make end-functional polymers including telechelics. The aliphatic telechelics enabled by olefin metathesis offer excellent toughness and moisture resistance. As one example of the potential benefit of such materials, the United States Navy has demonstrated that aliphatic telechelic diols, made using Grubbs catalyst, can be used to produce nontoxic, antifouling urethane coatings for marine applications [33]. Medtronic has also demonstrated the utility of such telechelics as components of polyurethane biomaterials for medical devices [34].



During the 1990s, researchers at Amoco Corporation (currently BP Amoco Corporation) developed difunctional telechelic polyolefins [35, 36] and demonstrated their use in making polyurethane elastomers [37]. Although Amoco patented a series of process patents involving traditional olefin metathesis catalysts [38], the company never commercialized the products and eventually donated the entire patent portfolio to Caltech, which had developed superior processes utilizing the well-defined Grubbs catalysts. Subsequent to the Amoco efforts, researchers at Bayer patented a family of end-functional polyolefins [39, 40] based on olefin metathesis processes [41] utilizing Grubbs catalyst, again primarily for application in new polyurethane compositions [42]. Materia is currently continuing development of a variety of functional telechelic polyolefins enabled by the ruthenium metathesis technology but has not yet begun marketing end products.

Several companies have been evaluating compositions based on functional ROMP polymers for dental applications. 3M ESPE (formed from the combination of 3M's Dental Products Division with ESPE Dental AG in 2000) has described both olefinic resin mixtures that can be cured via ROMP [43] and unsatu-

rated, functional ROMP oligomers that can be cured by radical initiators with low shrinkage [44]. Researchers at Ivoclar Vivadent have reported similar ROMP polymers/oligomers that are particularly useful as a constituent of dental adhesives [45]. Kerr Corporation, founded in 1891 and now a subsidiary of Sybron Dental Specialties, has developed norbornene-terminated polydimethylsiloxane compositions that are curable via ruthenium-catalyzed ROMP [46]. Compared with current platinum-catalyzed silicone dental impression materials, the ROMP-based systems from Kerr are not sensitive to sulfur-containing impurities present in the latex gloves now commonly worn by dentists.

Quintessence Biosciences, Inc. is an early-stage pharmaceutical company engaged in developing multivalent drugs based largely on ROMP technology licensed from the University of Wisconsin-Madison. In particular, Quintessence's Neobiopolymer™ technology, which provides the company's foundation for the synthesis of multivalent drugs, was developed by Professor Laura L. Kiessling [47–49] (see Chapter 3.6). Quintessence sees metathesis as a “key tool” for the controlled synthesis of the selectively functionalized linear polymers that it uses to produce its multivalent arrays [50].

Other selectively functionalized ROMP polymers enabled by the new generation of well-defined ruthenium olefin metathesis catalysts are currently under fairly intense scrutiny, if not yet commercialization, for a variety of combinatorial chemistry and life sciences applications. Professor Anthony G. M. Barrett at the Imperial College of Science, Technology, and Medicine has developed an entire class of ROMPgel reagents for combinatorial chemistry applications [51] (see Chapter 2.10). Professor Michael Buchmeiser at the University of Innsbruck has demonstrated a variety of ROMP monoliths useful as both catalyst supports [52] and separation media [53] (see Chapter 3.7). Professor Paul Hanson at the University of Kansas, partially in conjunction with Daniel Flynn (originally with Neogenesis Pharmaceuticals, Inc. and most recently with Deciphera Pharmaceuticals, Inc.), has also recently reported several ROMP-based methodologies of significance for combinatorial synthesis [54].

3.12.6

Hydrogenated ROMP Polymers

Since the commercial introduction of cyclic olefin copolymers (COCs) such as Zeon's Zeonex® and Zeonor® and Ticona's Topas® products, there has been increasing interest in high-performance hydrocarbon polymers obtained via the hydrogenation of ROMP polymers, the method of choice for producing completely amorphous COCs. Although Zeon's commercial products are made using traditional catalysts, the company has recent patent activity involving ruthenium systems [55]. In addition, several other companies that use well-defined catalysts have staked claims in this area, including Bayer [56], primarily for the transparency aspects of these polymers, and IBM [57], primarily because the chemical and electronic properties of these polymers make them potentially useful as photoresists.

3.12.7

Depolymerization

Because olefin metathesis is a reversible process, polymer depolymerization can be effected under the proper conditions. Academically, both Grubbs [58] and Wagener [59] have demonstrated metathetical polyolefin depolymerization using Grubbs catalysts. Industrially, Bayer has recently reported the use of a metathetical depolymerization process [60], using well-defined catalysts such as Grubbs catalysts, to prepare low-molecular-weight nitrile rubbers (NBRs) [61] and low-molecular-weight-hydrogenated nitrile rubbers (HNBRs) [62]. Materia is evaluating the utility of metathesis depolymerization of olefinic polymers and rubbers for both recycling and as a potentially inexpensive source of raw material for telechelic materials.

3.12.8

Summary

The newest generation of well-defined olefin metathesis catalysts, especially those based on ruthenium, offers an extremely promising combination of high reactivity combined with ease of handling and functional group tolerance. Although these catalysts are still relatively young and have yet to achieve significant commercial potential, they finally appear to have achieved a level of performance that will ensure their use in a variety of commercial polymer applications.

References

- 1 Vestenamer[®] is a registered trademark of Degussa AG.
- 2 Norsorex[®] is a registered trademark of Elf Atochem S.A.
- 3 Metton[®] is a registered trademark of Metton America, Inc.; Telene[®] is a registered trademark of APT, LLC; and PentamTM is a trademark of Zeon Corporation.
- 4 NGUYEN, S. T.; JOHNSON, L. K.; GRUBBS, R. H. Ring-Opening Metathesis Polymerization (ROMP) of Norbornene by a Group VIII Carbene Complex in Protic Media, *J. Am. Chem. Soc.*, **1992**, *114*, 3974–3975.
- 5 GRUBBS, R. H.; JOHNSON, L. K.; NGUYEN, S. T. Ruthenium and Osmium Metal Carbene Complexes for Olefin Metathesis Polymerization, U.S. Patent No. 5,312,940; May 17, 1994.
- 6 SCHWAB, P.; GRUBBS, R. H.; ZILLER, J. W. Synthesis and Applications of $\text{RuCl}_2(=\text{CHR}')(\text{PR}_3)_2$: The Influence of the Alkylidene Moiety on Metathesis Activity, *J. Am. Chem. Soc.*, **1996**, *118*, 100–110.
- 7 GRUBBS, R. H.; SCHWAB, P.; NGUYEN, S. T. High Metathesis Activity Ruthenium and Osmium Metal Carbene Complexes, U.S. Patent No. 6,111,121; August 29, 2000.
- 8 SCHOLL, M.; TRNKA, T. M.; MORGAN, J. P.; GRUBBS, R. H. Increased Ring Closing Metathesis Activity of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with Imidazolin-2-ylidene Ligands, *Tetrahedron Letters*, **1999**, *40*, 2247–2250.
- 9 WESKAMP, T.; KOHL, F. J.; HIERINGER, W.; GLEICH, D.; HERRMANN, W. A. Highly Active Ruthenium Catalysts for Olefin Metathesis: The Synergy of N-Heterocyclic Carbenes and Coordinatively Labile Ligands, *Angew. Chem., Int. Ed.*, **1999**, *38*, 2416–2419.

- 10 HUANG, J.; STEVENS, E. D.; NOLAN, S. P.; PETERSEN, J. L. Olefin Metathesis-Active Ruthenium Complexes Bearing a Nucleophilic Carbene Ligand, *J. Am. Chem. Soc.*, **1999**, *121*, 2674–2678.
- 11 SCHOLL, M.; DING, S.; LEE, C. W.; GRUBBS, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands, *Organic Letters*, **1999**, *1*, 953–956.
- 12 www.cymetech.com
- 13 WARNER, M. W.; DRAKE, S. D.; GIARDELLO, M. A. Metathesis Polymerized Olefin Composites Including Sized Reinforcement Material, U.S. Patent No. 6,040,363; March 21, 2000.
- 14 WARNER, M.; GIARDELLO, M. A. Process of Making Metathesis Polymerized Olefin Articles Containing Flame-Retarding Agents, U.S. Patent No. 6,071,459; June 6, 2000.
- 15 e.g., AOKI, T.; YAMAZAKI, H.; KAWAI, H.; INOUE, Y.; YASU, K.; FUJITA, T.; KATO, S.; SUZUKI, M. Electronic Device, WIPO International Publication No. WO 00/51178; August 31, 2000.
- 16 www.materia-inc.com
- 17 GIARDELLO, M. A.; LASCH, J. G.; CRUCE, C. J.; MACLEOD, J. G.; HAAR, C. M. Polyolefin Compositions Having Variable Density and Methods for Their Production and Use, U.S. Patent No. 6,525,125; February 25, 2003.
- 18 GIARDELLO, M. A.; HAAR, C. M. Metathesis-Active Adhesion Agents and Methods for Enhancing Polymer Adhesion to Surfaces, U.S. Patent No. 6,409,875; June 25, 2002.
- 19 CRUCE, C. J.; FILICE, G. W.; GIARDELLO, M. A.; STEPHEN, A. R.; TRIMMER, M. S. Infusion of Cyclic Olefin Resins into Porous Materials, WIPO International Publication No. WO 03/020504; March 13, 2003.
- 20 (a) TOKAS, E. F.; CASTER, K. C.; WEIH, M. A. Contact Metathesis Polymerization, WIPO International Publication No. WO 02/26857; April 4, 2002.
(b) TOKAS, E. F.; CASTER, K. C.; WEIH, M. A. Contact Metathesis Polymerization, WIPO International Publication No. WO 02/26858; April 4, 2002.
- 21 TOKAS, E. F.; CASTER, K. C. Improved Fiber Substrate Adhesion and Coatings by Contact Metathesis Polymerization, WIPO International Publication No. WO 01/077078; October 3, 2002.
- 22 KENDALL, J. L.; CASTER, K. C. Metathesis Polymerization Adhesives and Coatings, WIPO International Publication No. WO 03/000764; January 3, 2003.
- 23 WHITE, S. R.; SOTTOS, N. R.; GEUBELLE, P. H.; MOORE, J. S.; KESSLER, M. R.; SRIRAM, S. R.; BROWN, E. N.; VISWANATHAN, S. Autonomic Healing of Polymer Composites, *Nature*, **2001**, *409*, 794–797.
- 24 WHITE, S. R.; SOTTOS, N. R.; GEUBELLE, P. H.; MOORE, J. S.; SRIRAM, S. R.; KESSLER, M. R.; BROWN, E. N. Multifunctional Autonomically Healing Composite Material, U.S. Patent No. 6,518,330; February 11, 2003.
- 25 HARRIS, K. M.; RAJAGOPALAN, M. Golf Ball Compositions with Microencapsulated Healing Agent, U.S. Patent Application Publication No. 2003/0013551; January 16, 2003.
- 26 HARRIS, K. M.; RAJAGOPALAN, M. Self Healing Polymers in Sports Equipment, U.S. Patent Application Publication No. 2003/0032758; February 13, 2003.
- 27 (a) SETIABUDI, F.; MÜHLEBACH, A.; NAGANUMA, Y. Curable Composition Comprising a Diels-Alder-Adduct of Cyclopentadiene and a Filler, U.S. Patent No. 6,100,323; August 8, 2000.
(b) HAFNER, A.; VAN DER SCHAAF, P. A.; MÜHLEBACH, A. Polymerizable Composition and Polymerization Method, U.S. Patent No. 6,277,935; August 21, 2001.
(c) PICCINELLI, P.; VITALI, M.; ZEDDA, A. ROMP with Alkoxy Ether Groups, U.S. Patent Application Publication No. 2002/0185630; December 12, 2002.
- 28 LAVOIE, G. G.; MACKENZIE, P. B. Copolymerization of Norbornene and Functional Norbornene Monomers, U.S. Patent No. 6,395,851; May 28, 2002.

- 29 LAVOIE, G. G.; MACKENZIE, P. B. Copolymers of Norbornene and Functional Norbornene Monomers, U.S. Patent No. 6,512,065; January 28, 2003.
- 30 <http://jazz.nist.gov/atpcf/prjbriefs/prjbrief.cfm?ProjectNumber=95-05-0041>
- 31 BANSLEBEN, D. A.; HUYNH-TRAN, T.-C. T.; BLANSKI, R. L.; HUGHES, P. A.; ROBERTS, W. P.; GRUBBS, R. H.; HATFIELD, G. R. Regio-Regular Copolymer and Methods of Forming Same, U.S. Patent No. 6,153,714; November 28, 2000.
- 32 BANSLEBEN, D. A.; HUYNH-TRAN, T.-C. T.; BLANSKI, R. L.; HUGHES, P. A.; ROBERTS, W. P.; GRUBBS, R. H.; HATFIELD, G. R. Regio-Regular Functionalized Polymeric Packaging Material, U.S. Patent No. 6,203,923; March 10, 2001.
- 33 BRADY, R. F.; PAWLIKOWSKI, G. T. Robust, Nontoxic, Antifouling Polymer, U.S. Patent No. 5,652,027; July 29, 1997.
- 34 BENZ, M. E.; BONNEMA, K.; DIDOMENICO, E.; HOBOT, C. M.; MILLER, D. L. Medical Devices Containing Segmented Polyurethane Biomaterials, WIPO International Publication No. WO 98/50086; November 12, 1998.
- 35 NUBEL, P. O.; YOKELSON, H. B. Difunctional Telechelic Linear Non-Crosslinked Polyolefins, U.S. Patent No. 5,559,190; September 24, 1996.
- 36 NUBEL, P. O.; YOKELSON, H. B. Difunctional Telechelic Linear Non-Crosslinked Polyolefins, U.S. Patent No. 5,731,383; March 24, 1998.
- 37 YOKELSON, H. B.; NUBEL, P. O.; BEHREND, R. T. Polyurethane Elastomers Prepared from Difunctional Telechelic Linear Non-Crosslinked Polyolefins, U.S. Patent No. 5,589,543; December 31, 1996.
- 38 (a) NUBEL, P. O.; MORLAND, R. B.; YOKELSON, H. B. Process for Preparation of Telechelic Difunctional Unsaturated Oligomers or Polymers by Acyclic Olefin Metathesis, U.S. Patent No. 5,403,904; April 4, 1995.
(b) NUBEL, P. O.; YOKELSON, H. B.; COHEN, S. A.; BEHREND, R. T.; BOUSLOG, W. G.; NELSON, J. P. Process for Preparing Linear Monofunctional and Telechelic Difunctional Polymers and Compositions Obtained Thereby, U.S. Patent No. 5,512,635; April 30, 1996. (c) NUBEL, P. O.; BAGHERI, V. Process for Preparation of Unsaturated Oligomers or Polymers by Acyclic Olefin Metathesis, U.S. Patent No. 5,519,101; May 21, 1996. (d) NUBEL, P. O.; YOKELSON, H. B. Process for Preparing Difunctional Telechelic Linear Non-Crosslinked Polyolefins, U.S. Patent No. 5,589,548; December 31, 1996. (e) NUBEL, P. O.; YOKELSON, H. B.; COHEN, S. A.; BOUSLOG, W. G. Process for Preparing Linear Monofunctional and Telechelic Difunctional Polymers and Compositions Obtained Thereby, U.S. Patent No. 5,621,047; April 15, 1997. (f) NUBEL, P. O.; YOKELSON, H. B.; FRYE, W. H.; LYNCH, T.-Y.; SATEK, L. C.; MCCONAGHY, G. A. Process for Preparation of Addition Products of Difunctional Telechelic Polyolefins from Cyclic Olefins by Olefin Metathesis Reaction, U.S. Patent No. 6,060,570; May 9, 2000. (g) NUBEL, P. O.; YOKELSON, H. B.; FRYE, W. H.; LYNCH, T.-Y.; SATEK, L. C.; MCCONAGHY, G. A. Process for Preparation of Addition Products of Difunctional Telechelic Polyolefins from Cyclic Olefins by Olefin Metathesis Reaction, U.S. Patent No. 6,143,851; November 7, 2000.
- 39 PETERS, M. A. End-Functionalized Polyolefin Prepared via Ring Opening Metathesis Polymerization in the Presence of a Novel Chain Transfer Agent, and a Process for the Preparation of the End-Functionalized Polyolefin via Ring Opening Metathesis Polymerization, U.S. Patent No. 6,476,167; November 5, 2002.
- 40 HAIDER, K. W.; CHAN, J. C.; JONSSON, E. H.; FRANZ, U. W.; PETERS, M. A.; TAYLOR, R. P. Polyurethane Polyolefins and Prepolymers Based on Hydroxy Functional Polybutadiene, U.S. Patent No. 5,990,340; November 23, 1999.
- 41 PETERS, M. A. Process for the Synthesis of Hydroxyl-End Group

- Functionalized Polybutadienes, U.S. Patent No. 6,391,978; May 21, 2002.
- 42 TAYLOR, R. P.; CHAN, J. C.; HAIDER, K. W.; JONSSON, E. H.; FRANZ, U. W.; PETERS, M. A. Composition and Process for Preparation of Thermoplastic Polyurethanes (TPU Based on a Polybutadiene Soft Segment), U.S. Patent No. 6,166,166; December 26, 2000.
- 43 BISSINGER, P. Dental Compositions Curable by ROMP, U.S. Patent No. 6,075,068; June 13, 2000.
- 44 BISSINGER, P. Dental Compositions Based on ROMP Oligomers and Polymers, U.S. Patent No. 6,147,136; November 14, 2000.
- 45 RHEINBERGER, V.; MOSZNER, N.; STELZER, F.; SCHITTER, R.; ZEUNER, F. Functionalized and Polymerizable Polymer, U.S. Patent No. 6,479,592; November 12, 2002.
- 46 ANGELETAKIS, C.; CHEN, M. Dental Impression Material Utilizing Ruthenium Catalyst, U.S. Patent No. 6,455,029; September 24, 2002.
- 47 KIESSLING, L. L.; MANNING, D. D.; MORTELL, K. H. Polyglycomers, U.S. Patent No. 5587442; December 24, 1996.
- 48 (a) KIESSLING, L. L.; STRONG, L. E. Methods for Making Multivalent Arrays, U.S. Patent No. 6,271,315; August 7, 2001. (b) U.S. Patent No. 6,538,072; March 25, 2003.
- 49 KIESSLING, L. L.; GORDON, E. J.; STRONG, L. E. Methods and Reagents for Capping Ruthenium or Osmium Carbene-Catalyzed ROMP Products, U.S. Patent No. 6,291,616; September 18, 2001.
- 50 STRONG, L. E.; KIESSLING, L. L. A General Synthetic Route to Defined, Biologically Active Multivalent Arrays, *J. Am. Chem. Soc.*, **1999**, *121*, 6193–6196.
- 51 BARRETT, A. G. M.; HOPKINS, B. T.; KÖBBERLING, J. ROMPgel Reagents in Parallel Synthesis, *Chemical Reviews*, **2002**, *102*, 3301–3324.
- 52 BUCHMEISER, M. R. Heterogeneous C–C Coupling and Polymerization Catalysts Prepared by ROMP, *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 1837–1840.
- 53 (a) MAYR, B.; TESSADRI, R.; POST, E.; BUCHMEISER, M. R. Metathesis-Based Monoliths: Influence of Polymerization Conditions on the Separation of Biomolecules, *Analytical Chemistry*, **2001**, *73*, 4071–4078. (b) BUCHMEISER, M. R.; SINNER, F. M. Method of Producing Monolithic Support Materials, WIPO International Publication No. WO 00/73782; December 7, 2000. (c) BUCHMEISER, M. R.; SINNER, F. M. Functionalized Supporting Materials Which Can Be Obtained by Means of Metathesis Graft Polymerization, WIPO International Publication No. WO 00/61288; October 19, 2000.
- 54 (a) HARNED, A. M.; HANSON, P. R. Capture-ROMP-Release: Application for the Synthesis of O-Alkylhydroxylamines, *Organic Letters*, **2002**, *4*, 1007–1010. (b) HARNED, A. M.; MUKHERJEE, S.; FLYNN, D. L.; HANSON, P. R. Ring-Opening Metathesis Phase-Trafficking (ROMpt) Synthesis: Multistep Synthesis on Soluble ROM Supports, *Organic Letters*, **2003**, *5*, 15–18. (c) MOORE, J. D.; HERPEL, R. H.; LICHTSINN, J. R.; FLYNN, D. L.; HANSON, P. R. ROMP-Generated Oligomeric Sulfonyl Chlorides as Versatile Soluble Scavenging Agents, *Organic Letters*, **2003**, *5*, 105–107.
- 55 TSUNOGAE, Y.; SAKAMOTO, M.; TOKORO, M.; TAGUCHI, K. Process for Producing Hydrogenated Ring-Opening Polymerization Polymer of Cycloolefin, U.S. Patent No. 6,486,264; November 26, 2002.
- 56 CHEN, Y.; DUJARDIN, R.; PIELARTZIK, H.; FRANZ, U. W. Process for the Production of Hydrogenated Ring-Opened Metathesis Polymers, U.S. Patent No. 5,932,664; August 3, 1999.
- 57 (a) JAYARAMAN, S.; VICARI, R.; RHODES, L. F.; VARANASI, P. R.; SOORIYAKU-MARAN, R.; ALLEN, R. D.; DIPIETRO, R. A.; ITO, H.; OPITZ, J. Norbornene Sulfonamide Polymers, WIPO International Publication No. WO 00/46268; August 10, 2000. (b) JAYARAMAN, S.; GOODALL, B. L.; VICARI, R.; LIPIAN, J.-H.; ALLEN, R. D.; OPITZ, J.; WALLOW, T. I. Polycyclic Polymers Containing Pendant Cyclic

Anhydride Groups, WIPO International Publication No. WO 00/53658; September 14, 2000.

- 58 GRUBBS, R. H.; NGUYEN, S. T. Polymer Depolymerization Using Ruthenium and Osmium Carbene Complexes, U.S. Patent No. 5,728,917; March 17, 1998.
- 59 WATSON, M. D.; WAGENER, K. B. Solvent-Free Olefin Metathesis Depolymerization of 1,4-Polybutadiene, *Macromolecules*, **2000**, 33, 1494–1496.
- 60 GUERIN, F.; GUO, S. X. Process for the preparation of Low Molecular Weight Hydrogenated Nitrile Rubber, WIPO International Publication No. WO 02/100905; December 19, 2002.
- 61 GUERIN, F.; GUO, S. X. Low Molecular Weight Nitrile Rubber, WIPO International Publication No. WO 03/002613; January 9, 2003.
- 62 GUERIN, F.; GUO, S. X.; SZENTIVANYI, Z.; GLANDER, S. Low Molecular Weight Hydrogenated Nitrile Rubber, WIPO International Publication No. WO 02/100941; December 19, 2002.

Index

Numbers in front of the page numbers refer to Volumes 1, 2, and 3, respectively: e.g., 2/254 refers to page 254 in volume 2.

a

- A,B-alternating copolymer 2/241
- ab initio* methods 1/23
- ABA triblock copolymer 3/256, 3/274
- A-B-A type 3/76
- AB multiblock 3/256
- A-B type 3/76
- ABA-type triblock copolymer 3/36, 3/58
- acetal functionality 3/270
- acetate-protecting group 2/290
- (5R,6S)-6-acetoxy-5-hexadecanolide 2/493
- acetoxy telechelic polybutadiene 3/268
- acetylene 1/53
- acetylene, disubstituted 3/124
- acetylene, monosubstituted 3/124
- acetylene polymerizations 1/54
- acrolein acetal 2/283
- acrylate dimerization 2/269
- acrylate ester 2/11
- acrylic amide 2/266
- acrylonitrile 2/264
- activation energy 1/148
- Acushnet Company 3/411
- acyclic 1/64
- acyclic cross-metathesis (ACM) 1/132, 1/156
- acyclic diyne metathesis (ADIMET) 3/354, 3/358
- acyclic metathesis 1/159
- α -addition 3/388
- π adduct 1/149
- adhesive 3/326
- ADMET 2/160, 2/478, 3/127, 3/258
- ADMET depolymerization 3/269
- ADMET polymerization 3/262
- Advanced Technology Program (ATP) 3/412
- AgClO₄ 2/196
- AgF 2/457
- aggregate 3/82
- aglycone 6-nor-fluivirucinin B1 2/73
- agostic 1/21, 1/24
- α agostic interaction 1/11
- agrochemical 2/506
- akagerine alkaloid family 2/51
- Akzo Nobel 2/497
- alcohols 2/274
- aldehyde 3/278
- ω -aldehyde-functionalized polymer 3/83
- aldol group transfer polymerization 3/15
- aldol reaction 2/296
- Alexakis 2/92
- aligned polyacetylene 3/132
- aliphatic telechelics 3/412
- alkaloid synthesis 2/344
- alkaloid total synthesis 2/350
- alkaloids 2/48
- alkane σ -bond metathesis 1/200
- (*E*)-alkene 2/456
- alkene-containing compounds 2/248
- alkene metathesis of enyne 3/363
- (*Z*)-alkene unit 2/443
- alkenyl phosphonate 2/316
- alkenylepoxyde 2/471
- alkenylsilane 2/463
- alkoxide 1/17
- alkoxide ligand 1/13
- alkoxide ligand exchange strategy 3/86
- alkyl chloride 2/386
- 3-alkyl-2,5-divinylthiophene 3/316
- alkylidene 1/8, 1/173, 1/174, 2/251
- alkylmetal 3/377
- alkyltitanium complex 3/87
- alkyne 1/177

- 1-alkyne 1/98
- alkyne cross-metathesis (ACM) 2/439
- alkyne metathesis 2/77, 3/128, 3/355
- alkyne metathesis polymerization 3/128
- alkyne trimerization 2/171, 3/356
- alkynyl ether 2/182
- allyl acetate 2/261
- allylamine 2/290
- allylbenzene 2/470
- allylboronate 2/272
- allylboronic acids 2/383
- allylchlorodimethylsilane 2/476
- allylic alcohols 2/260
- L-allylglycine 2/159
- allylic-substituted diene 3/305
- allylnitrile 2/212
- allylsilane 2/254, 2/463
- allylsulfide 1/37
- allylsulfonamides 2/35
- allyltributyltin 2/395
- allyltrimethylsilane 2/217
- allyltrimethylsilane 2/340, 2/470, 2/476
- alternating alkylidene mechanism 2/213
- alternating copolymer 3/103, 3/168, 3/309
- alternating ring-opening metathesis copolymerization 3/105
- Alzheimer's disease 2/498
- ambrettolide 2/443
- Amgen 2/500
- amidoximes 2/382
- amine 2/384
- amino acid 3/189, 3/191
- 4-amino-azepin-3-one 2/499, 2/500
- Amoco Corporation 3/412
- amphidinolide A 2/309
- amphiphilic block copolymer 3/98
- amphiphilic sphere 3/101
- amphiphilic star-block copolymer 3/102
- amyloid protein 2/498
- anaferine 2/163
- ancillary ligands 1/11, 1/77, 1/116
- anionic polymerization 3/257
- anolignane A 2/199
- anolignane B 2/199
- ansa-heteroferrocene 2/429
- ansa-metallocene catalysts 2/425
- anti* 1/21
- antibiotic 3/195, 3/213, 3/220
- anti*-Bredt alkenes 2/29
- anticancer 2/353
- antifouling urethane coating 3/412
- anti-HIV activity 2/303
- anti-osteoporosis activity 2/497
- antitumor 2/328
- APT 3/409
- aqueous media 3/57
- aqueous ROMP 3/53, 3/55
- aqueous suspension 3/53
- arabinofuranosides 2/8
- ARCM of 1,7-dienes 2/132
- Arduengo 1/80
- Argogel 2/363
- Arimoto 3/196, 3/213
- Armstrong 3/118
- aromatic system 2/170
- aryloxy 1/44
- 4a-aryloxydecahydroisoquinolines 2/503
- (+)-Aspicilin 2/72
- asteriscanolide 2/19, 2/232
- (+)-asteriscanolide 2/75, 2/303
- asymmetric catalysts 1/27
- asymmetric desymmetrization 2/94
- asymmetric induction 2/134
- asymmetric RCM (ARCM) 2/94, 2/129
- asymmetric ring-closing metatheses (ARCM) 2/228
- asymmetric ring-opening cross-metatheses (AROCM) 2/228
- asymmetric ring-opening metathesis (AROM) 2/129, 2/137
- atom transfer radical polymerization (ATRP) 3/257, 3/277
- atropdiastereoselectivity 2/313
- atropisomer 2/313
- ATRP 3/88, 3/94, 3/272
- ATRP support 3/235
- Au-immobilized ligand 3/230
- australine 2/50
- average functionality (F_n) 3/261, 3/263
- (+)-axenol 2/23
- azabicyclic ring 2/339
- azabicyclo[*n*.3.1]alkene 2/340
- azacrown-ether 2/67
- aziridine 2/305
- b**
- backbiting 1/149, 3/10, 3/13
- backbiting reaction 3/59, 3/123, 3/260
- backbiting/chain-transfer 3/271
- backbone flexibility 3/81
- backpressure 3/244
- bacterial chemotaxis 3/216, 3/219f
- bafilomycin 2/306
- balanol 2/49
- Banwell 2/72
- barralene 3/136
- Barrett 2/81, 2/379f, 2/386, 2/501, 3/230, 3/237, 3/413

- barrier properties 3/412
 Barton 2/380
 baseball 3/410
 basicity 1/117
 Basset 2/211
 Bayer 3/412ff
 Bazan 3/63, 3/315
 Beer 2/101
 benzaldehyde 1/120
 benzoazocine 2/344f, 2/345
 benzobarrelene 3/135, 3/158
 benzocrown ether 3/73
 benzophenone 3/278
 benzoxepine 2/40
 benzvalene 3/133
 benzylcarbene 1/99
 Bernoullian 3/310
 Bespalova 2/212
 BET measurement 3/228
 bicyclic alkenes 2/219
 bicyclic lactam 2/349
 bicyclic β -lactam 2/81
 [5.4.0] bicyclic ring 2/165
 bicyclo[2.2.2]octadiene 3/37
 bicyclo[3.2.0]hept-1-ene 3/164
 bicyclo[3.2.0]hept-6-ene 3/49
 bicyclo[4.2.0]oct-7-ene 3/49
 bidentate phosphines 1/70
 bidentate Schiff base 1/122
 bifunctional 1/142
 bimetallic 1/122
 bimetallic ruthenium catalysts 3/58
 bimetallic ruthenium initiator 3/90
 bimolecular decomposition 1/119
 bimolecular formations 1/183
 binaphtholate 1/26
 binaphtholate catalyst 3/169
 binol-based complex 2/132
 bioactive polymer 3/183
 bioactive polymer synthesis 3/183
 Biochem Pharma 2/505
 biological application 3/345
 biologically active epitope 3/180ff, 3/200
 biologically active material 3/186, 3/220
 biomaterial 3/191
 bioorganic 2/275
 bioorganic systems 2/278
 biorelevant polyether 3/74
 Birch-type reduction 2/443, 2/459
 bis(*N*-alkylenedicarboxyimidonorborene)
 3/107
 bis(cyclopentadienyl) titanacyclobutane 3/11
 bis(di-*tert*-butylphosphanyl)methane 1/120
 bis(molybdenum alkylidene) 3/33
 bisphenol-A 3/323
 bis(siloxy) complexes 1/194
 bis(stibine) 1/97
 2,3-bis(trifluoromethyl)-norbornadiene 3/22,
 3/168f
 bite angle 1/145
 Blechert 2/9, 2/27, 2/64, 2/94, 2/217f, 2/224,
 2/362, 2/375, 2/377, 2/476f
 block copolymer 1/43, 2/429, 3/4, 3/14f,
 3/59, 3/226, 3/384, 3/389
 block copolymer synthesis 3/58
 Boehringer Ingelheim 2/496
 Boger 2/308, 2/373
 Bolm 2/391
 Boncella 2/405
 bond fission 2/194
 boomerang catalyst 1/77, 2/375
 9-borabicyclononane 3/265
 borane 3/266
 boric ester 2/193
 boron aldol methodology 2/302
 boronate 2/81, 3/320
 boron-heterocycles 2/37
 boronic acid 2/383
 (+)-boronolide 2/302
 bottlebrush-type shape 3/98
 Branch content 3/340
 brefeldin A 2/315
 (+)-brefeldin 2/286
 brevetoxin B 2/43, 2/46, 2/323
 brevetoxins 2/43
 bridged bicyclic alkenes 2/218
 bridged bicycloalkenes 2/24
 Bristol-Myers Squibb 2/497, 2/499
 bromindole 2/346
 Brookhart's acid 1/106
 Brzezinska 3/274
 Buchmeiser 2/377, 2/393, 3/413
 Burke 2/163, 2/474
 Buszek 2/19
 1,3-butadiene 3/312
 1-butene 1/50, 1/146, 1/149, 1/158
 2-butene-1,4-diol 3/275
- c**
- cadmium selenide particle 3/237
 Calderon 2/206, 3/7, 3/284, 3/331
 calix[4]arene 2/66
 calixarenes 2/373
 cancer therapy 3/63
 capillary electrochromatography 3/241
 $\Delta^{9(12)}$ -cannabinene 2/2
 capture-ROMP method 2/395
 carbacephem 2/198

- carbapenem skeleton 2/198
- carbazoyl-substituted polymer 3/79
- carbene 2/177
- carbocycles 2/18
- carbocyclic 2/474
- carbocyclic nucleosides 2/8
- carbocyclization 2/7, 2/10, 2/27
- carbohydrate 3/183f, 3/186f, 3/198, 3/203f, 3/208, 3/220
- carbohydrate annulation 2/17
- carbohydrate-based polymer 3/79
- carbohydrate-substituted polymer 3/183, 3/185, 3/187, 3/198
- carbon monoxide copolymer 3/344
- carbonyl hydride 1/127
- α -carbonyl olefin substrates 2/13
- β -carbonyl olefin substrates 2/13
- carbostannane 3/329
- carboxylic acid 3/383
- carbyne 1/92
- carbynehydridoruthenium complex 2/224
- carbynes 1/106
- carcinoma 2/307
- Carothers equation 3/289
- Casey 1/48, 1/52, 3/8f
- Casey carbene 2/483, 3/380
- Cassidy 2/473
- castanospermine 2/51
- Caster 3/238
- catalyst commitment 1/167
- catalyst initiation 1/117
- catalyst leaching 1/77
- catalyst loading 2/7
- catalyst modularity 2/131
- catalyst precursor 3/354
- catalytic asymmetric olefin metathesis 2/128
- catalytic asymmetric synthesis 2/133
- catalytic enantioselective method 2/135
- catalytic enantioselective variant of the ROCM 2/229
- catalytically resolved 2/128
- catenane 2/97, 2/98, 2/100
- [2]catenane 2/97, 2/99, 2/104
- catenane synthesis 2/410
- cathepsin K 2/499
- cation-anion interaction 3/173
- cationic 3/4
- cationic Rh 3/382
- cationic ruthenium complexes 3/172
- Caulton 1/67, 1/100
- CbzNB 3/80
- C–C activation 1/200
- CCl_4 , used as a solvent 3/379
- CdSe nanocluster 3/82
- cell adhesion 3/345
- cell-cell clustering 3/216
- cellular adhesion 3/211
- cellular binding assay 3/278
- ceramic materials 2/478
- C_2F_4 1/91
- C–H activation 1/200
- chain elongation 2/283
- chain extension/elongation 2/282
- chain polymerization 3/2
- chain transfer 3/10, 3/12, 3/20, 3/61, 3/259
- chain-growth metathesis polymerization 3/128
- chain-growth polymerization 3/4
- chain-propagating 3/13
- chain-transfer 3/59
- chain-transfer agent 3/111, 3/248, 3/258f, 3/412
- changing the solvent 2/358
- Chasmawala 3/265
- Chatani 2/180, 2/194
- Chaudret 1/99f
- Chauvin 1/6, 1/8, 1/33, 1/51, 2/206, 2/209, 3/7, 3/9, 3/285, 3/290
- Chauvin mechanism 2/169, 2/207, 3/182
- chelate 3/300
- chelate complexes 3/334
- chelating 1/120
- chelating alkylidene 1/70
- chelating diamide substituted norbornene 3/82
- chelating diene 3/157
- chelating effect 1/123, 2/154, 2/266
- chelating ligand 2/494
- chelation 2/11, 3/51
- chemically tagged 2/386
- chemoselective 2/290
- chemoselectivity 2/270, 2/455
- chemotherapeutics 3/191
- chiral 3/399
- chiral Biphen-Mo catalysts 2/130
- chiral catalysts 1/129
- chiral heterocyclic 2/157
- chiral HPLC 3/231
- chiral ligand 3/174
- chiral Mo-based complexes 2/130
- chiral monodentate N-heterocyclic carbene ligand 2/145
- chiral motif 1/129
- chiral optically pure catalysts 2/128
- chiral polymer 3/399
- chiral polyolefin 3/345
- chiral rhenium fragment 2/414
- chiral Ru catalysts 2/145

- chiral Ru-based carbene 2/146
 chlorambucil 3/196
 Christian 1/108
 Chromenes 2/88
 chromium Fischer carbene 2/270
 chromophore 3/155
 Chung 3/265f
 Ciba 3/412
 ciguatoxin 2/43, 2/45, 2/87
 cinnamaldehyde 2/495
cis olefin 2/264
cis or *trans* double bonds 1/25
cis-2,6-divinyl piperidines 2/341
cis-2-pentene 1/14
cis-cyclooctene 1/104
cis-to-*trans* isomerization 3/146
 citreofuran 2/457
 civetone 2/443
 Claisen chemistry 2/263
 Claisen rearrangement/RCM 2/296, 2/474
 Claisen-Ireland reaction 2/2
 Clark 2/42, 2/87, 2/182
 classical catalyst 3/284
 classical heterogeneous 1/201
 clipping 2/101
 CM 2/316
 CmD 3/107
 CM product selectivity 2/269
 C-neoglycopeptides 2/280
¹³C NMR analysis 3/298
 CO 1/120
 co-ADIMET 3/365
 cocaine 2/342
 co-catalyst 1/74, 3/387
 COD/acetal copolymer 3/74
 COE 1/147
 coleophomone 2/332
 comb graft copolymer 3/92
 combinatorial 2/275
 combinatorial application 3/1
 combinatorial chemistry 2/361, 2/364, 2/399, 3/249, 3/413
 combinatorial library 2/420, 2/505
 combinatorial synthesis 3/413
 comb-shaped polymer structure 3/4
 commodity materials 2/492
 π -complex formation 1/150
 complex organic molecules 2/252
 composite 3/238, 3/411
 compressed (liquid or supercritical) CO₂ 3/383
 concanavalin A 3/204
 condensation polymerization 3/288
 cone angle 3/47
 conformational constraints 2/21, 2/70
 conjugated diolefinic substrate 2/75
 π -conjugated olefin 2/266
 conjugated polymer 3/118, 3/129, 3/360
 conjugated polymer, cationically modified 3/134
 Conner 3/65
 contact metathesis polymerization (CMP) 3/411
 continuous matrix 3/242
 control of molecular weight 3/6, 3/92
 controlled polymerization 3/4
 controlled ROMP 3/19
 Cook 2/49
 coordinating 2/48, 2/112
 coordination of the electron-rich functional group 3/317
 Cope rearrangement 2/216, 2/304
 copolymer 3/72
 copolymer shell 2/406
 copolymerization 3/157
 copolymers of cyclooctatetraene with 1,5-cyclooctadiene and norbornene 3/124
 copolymers of polyphosphazene 3/95
 corrosion resistance 3/408
 corrosion-resistant composite piping 3/410
 Coughlin 3/237, 3/331
 covalent capture strategy 2/62
 Cp* ligand 3/162
 Cp₂MoCl₂ 3/379
 Cr alkylidene 1/197
 Crimmins 2/8, 2/40, 2/299
 cross product 2/258
 cross-coupling 2/252
 cross-link density 3/108
 cross-linked polymer 3/105, 3/110, 3/296
 cross-linked rubber 3/256
 cross-linking 3/318
 cross-linking effect on the physical properties of polymer 3/108
 cross-metathesis 2/314, 2/332, 2/470, 3/7
 cross-propagation reaction 3/73
 Crowe 2/470
 Cryovac 3/412
 CS₂ 1/87
 c/t blocky 3/157, 3/161
 c/t ratio 3/146
 Cuny 2/221
 cyclic 1-amino, 1-carboxylic acid 2/199
 cyclic alkenylboronates 2/37
 cyclic amino acids 2/54
 cyclic boronic ester 2/193
 cyclic enol ethers 2/42
 cyclic inhibitors 2/58

- cyclic olefinic phosphonates 2/33
 cyclic oligomers 3/262
 cyclic peptide 2/55, 2/61, 2/363
 cyclic phosphazene 3/320
 cyclic trisubstituted alkenes 1/52
 cyclic α -amino acid 2/88
 cyclic α -thiophosphonates 2/36
 cyclin-dependent kinases 2/499
 cycloalkyne 2/443, 2/451
 cyclobutadiene 3/355
 cyclobutene 1/52, 1/65, 2/163, 2/178, 2/213, 2/476, 3/35, 3/51, 3/158, 3/164
 cyclobutenyl alkene 2/138
 cyclocarbosilane 2/479
 cyclodextrin 2/66
 β -cyclodextrin-grafted monolith 3/250
 cycloheptatriene 2/231
 1,3-cyclohexadiene 2/172
 cyclohexene 2/156, 2/187, 2/243
 cyclohexenyl ethers 2/140
 cyclometallation 1/37, 1/44
 cyclooctadiene 1/73, 3/267
 1,5-cyclooctadiene 2/484
 cyclooctadiene/4,7-dihydro-1,3-dioxepin 3/270
 cyclooctatetraene 3/122, 3/126
 cyclooctatetraene, copolymers 3/124
 cyclooctatetraene, monosubstituted 3/124
 cyclooctene 1/147, 2/240, 2/477, 2/482
 5-cyclooctene-*trans*-1,2-diol 3/412
 cyclopentadienyl 1/178
 cyclopentene 1/142, 1/149, 2/240, 2/243, 3/42
 1,4-cyclopentene-*cis*-diol 2/158
 cyclopentenyl phosphonates 2/501
 cyclopentylidene 1/36
 cyclopolymer 2/86
 cyclopropane 1/2, 2/473
 cyclopropene 1/63, 2/223
 cyclopropenone ketal 2/476
 η^3 -cyclopropenyl 1/182
 cyclorelease 2/366ff
 cyclorelease strategy 2/328
 cyclorelease/macrolactonization 2/369
 (–)-cylidrocyclophanes 2/109
 cylindrocyclophanes A and F 2/314
p-cymene 1/74
 Cymetech, LLC 3/410
 Cyonyx® 3/410
 cytotoxicity 2/298, 2/309
- d**
- (±)-dactylol 2/17
 d⁰ alkylidene complexes 1/12
 Danishefsky 2/75, 2/115, 2/497
 DCPD 3/411
 dcpe 1/144, 1/148
 De Brabander 2/306
 1,9-decadiene 2/482, 3/293, 3/296ff, 3/310, 3/313f, 3/321, 3/323, 3/334, 3/347
 5-decenyl acetate 2/492
 decomposition 1/22, 1/71, 3/57
 defined porosity 3/242
 deformed 3/399
 degenerate metathesis 3/294
 degenerate olefin metathesis 1/161
 degradation 2/485, 3/266, 3/277
 dehydrochlorination of PVC 3/137
 α,α -dehydrogenation 1/175
 dehydrogenative silylation 2/465
 dehydrohomoancepsenolide 2/438
 Deming 3/274
 dendrimer 2/97, 2/98, 2/109, 3/100
 dendrimer-like hexakis (pincer) complex 2/428
 dendritic catalyst 2/377
 dendrobatid alkaloid 2/155
 Denmark 2/31, 2/473
 density functional methods 1/24
 density functional theory (DFT) 1/23, 1/105
 dental adhesives 3/413
 dental application 3/412
 deoxyribonucleic acid (DNA) 3/193
 depolymerization 3/270, 3/292, 3/330
 derivatives of polyethylene 3/74
 desymmetrization 2/133, 2/475
 desymmetrizing 2/151
 deuterium crossover experiment 2/213
 deuterium-labeled 2/466
 DFT studies 1/129
 diacetate 2/261
 1,4-diacetoxy-*cis*-2,3-butene 2/262
 diacrylate monomer 3/103
 diads 3/27
 dialkoxy-substituted PPEs 3/360
 dialkyl(di(propynyl))benzene, random copolymer 3/370
 2,5-dialkyloxy-1,4-divinylbenzenes 3/315
 dialkyl-PPEs 3/360
 diallyl metallocene dichlorides 2/422
 diallylamine 3/319
 diallyldimethylsilane 2/481
 diastereoselective cyclization 2/315
 diastereoselective metathesis 2/94
 diastereoselectivities 2/256
 diazoalkane 1/65, 1/95
 diazomethane 1/88, 1/95

- diazo-transfer 1/65
 diblock copolymer 3/387
 dicationic ruthenium 1/107
 2,3-dichloro-5,6-dicyanoquinone (DDQ) 3/135
 dicobalt hexacarbonyl alkyne complexes 2/420
 dicyclopentadiene (DCPD) 1/64, 1/104, 3/105, 3/242, 3/408
 di(dodecyldipropynyl)fluorene 3/368
 dielectric constant 3/155, 3/334
 dielectric property 3/155
 Diels-Alder reaction 2/25, 2/81, 2/83, 2/92, 2/151, 2/168, 2/172, 2/185, 2/296, 2/312, 2/386
 1,3-diene 2/189
 α,ω -diene 2/330, 2/338
 dienyne metathesis 2/83
 diethyl diallylmalonate 1/73
 (\pm)-differolide 2/199
 difluorocarbene 1/92
 difunctional telechelic polyolefin 3/412
 dihalocarbene 1/92
 di-5-hexenyl ether 3/334
 di-5-hexenylsulfide 3/321
 dihydrocarboline 2/348
 dihydrocorynantheol 2/347
 dihydrocuscohygrine 2/163
 dihydrofuran 2/158, 2/168
 2,5-dihydrofuran 3/318
 6,7-dihydro-2(3H)-oxepinone (DHO2) 3/75
 dihydropyran 2/299, 2/368
 dihydropyrrolylacetophenone 1/56
 diimide 2/358
 diimide reduction 3/338
 diisocyanate 3/331
 1,4-diisopropenylbenzene 3/314
 3,4-diisopropylidenecyclobutane 3/126
 Dijkstra 2/428
 dimerization 2/278
 dimerize 2/330
 dimetallatetrahedrane 1/179
 4-(*N,N*-dimethylamino)pyridine (DMAP) 3/389
 3,3-dimethylcyclobutene 3/40
 2,9-dimethyl-1,5,9-decatriene 3/305
 dimethyldivinylsilane 3/325
 2,5-dimethyl-1,5-hexadiene 3/305
 dimethyl 3-hexenedioate 3/264
 4,4-dimethylpentene 2/217
 2,6-dimethylphenoxo (dmp) Nb complex 3/381
 dimethyltitanocene 2/3
 dimethylvinylalkylidene 1/67
 dinorbornenyl telechelic polyphosphazene 3/95
 dinuclear Rh complex 3/382
 dioctyl-2,7-divinylfluorene 3/315
 Diodes 3/125
 dioxygen 1/120
 di-4-pentenyl sulfide 3/334
 1.1-diphenylcyclopropane 1/97, 1/99
 diphenyldiazomethane 1/97
o,o'-diphenylphenoxy ligand 1/37
 1,2-dipropenylbenzene 3/313
 1,3-dipropenylbenzene 3/313
 1,4-dipropenylbenzene 3/313
 3,3-di-*n*-propylcyclobutene 3/40
 di(propynyl)fluorenone 3/368
 dipropynylated stilbene 3/364
 direct injection molding (RIM) 3/408
 direct olefin stereoselectivity 2/254
 direct synthesis of polyacetylene 3/376
 disaccharide 3/187
 discovery engine 2/356
 disilylenevinylene 2/483
 disproportionation 2/464
 dissociation 1/72
 dissociative mechanism 1/178
 dissociative pathway 1/113
 dissociative processes 1/138
 disubstituted acetylene 3/378, 3/381
 disubstituted alkene 2/183
 3,3-disubstituted cyclopropene 1/65
 disubstituted olefine 2/259
 1,1-disubstituted olefine 2/263
 1,1-disubstituted-1-silacyclopent-3-enes 2/483
 disulfide 2/364
 disulfide bond 2/311
 disulfur ligands 2/415
 disulfur-containing cyclic carbene 1/87
 ditelechelic 3/255
 dithiothreitol 2/364
 Diver 2/172, 2/193
 diversification tool 2/372
 diversity-oriented organic synthesis 2/163
 diversity-oriented synthesis 2/365
 1,2-divinylbenzene 3/314
 1,4-divinylbenzene 3/313
 1,4-divinylcyclohexene 3/303
 divinyl ketone 2/239
 divinylsilane 3/316
 diyne 2/449
 1,6-diyn 2/171
 DMF 1/120
 DMSO 1/120
 DNA 3/194
 11-docosene 2/493

- 2,10-dodecadiene 3/312
 domino 2/162
 domino metathesis 2/478
 domino reactions 2/151
 donor strength 1/124
 doped polyacetylene 3/375
 doping of conjugated polymers 3/368
 Dötz 2/420
 Dötz reaction 1/54, 1/56
 double stranded (ds) DNA 3/250
 double-bond triad sequences 3/148
 double-helix structure 2/428
 Dow 2/494
 Dowden 2/377
 Down's syndrome 2/498
 drug/polymer conjugate 3/195
 drug-delivery vehicles 3/4
 dtbpe 1/144, 1/148
 dtbpm 1/121
 dumbbell-shaped copolymer 3/102
 DuPont 1/61, 2/497f, 2/504
 Durham precursor 3/133
 Durham precursor route to polyacetylene 3/129
 Durham route 3/145
 dyad units 3/143
 dyad, isotactic 3/144, 3/154
 dyad, syndiotactic 3/144, 3/154
 dynamic combinatorial chemistry 2/107, 2/373
 dynamic combinatorial screening 2/332
 dynamic mechanical analysis (DMTA) 3/108
 dysinosin A 2/9
- e**
 Eastman Chemical 3/412
 Eastman's EpB® oxirane 3/412
 Easton Sports 3/410
E. coli 3/216, 3/219
 Edison 3/118
E,E-isomer 2/218
 effector 3/205, 3/216
 11-eicosenyl acetate 2/492
 eight ring-opening metathesis 2/501
 eight-membered rings 1/65
E-isomer 2/358
 electrical and optical properties 3/130
 electrical properties of polyacetylene 3/120
 electrocyclic reaction 1/56
 electroluminescence properties 2/480
 electroluminescent material 2/276
 14-electron 1/143
 14-electron complex 1/140
 electron-deficient olefin 2/257, 2/302
 electron-donating phosphine 1/64
 electronic 3/410
 electronic influence 1/156
 π electronic structure 3/119
 14-electron intermediate 1/72
 16-electron olefin complex 1/72
 electron-poor 1/125
 14-electron species 1/102
 electron-withdrawing anions 1/64
 electrospray ionization (ESI) 1/135
 electrospray ionization mass spectrometry 1/132
 Eli Lilly 2/499
 emissive polymer 3/85
 Emrick 3/237
 emulsion 3/53f, 3/187, 3/207f
 Enanta Pharmaceuticals 2/496
 enantiocontrol 2/131
 enantiodifferentiation 2/137
 enantiomeric excesses 2/392
 enantiomerically 1/25f
 enantiomorphic site model 3/174
 enantiomorphic site-control mechanism 3/32
 enantioselective 2/157, 2/506
 enantioselective ring 1/26
 enantioselective ring-opening/cross-metathesis reactions 2/147
 enantioselective ROCM 2/228
 enantioselective synthesis of 8-membered ring amines 2/136
 enantioselective total synthesis 2/134
 encapsulated 3/240
 end-capping 3/183, 3/199, 3/293
 end-capping reaction 3/257
 end-capping reagent 3/263
 end-functional polyolefin 3/412
 end-functionalized 3/83
 end-functionalized polymers 3/384
 end-labeled material 3/200f
 end-labeled multivalent ligand 3/200
endo-brevicomine 2/134
endo-dicyclopentadiene 3/157
 ene-diene systems 2/76
 energy surface 1/160
 energy traps 3/369
 enhanced biostability 2/311
 Enholm 2/394f
 enoic carbene 2/243
 enol ethers 2/42
 entropic barrier 3/296
 enyne 1/56, 2/164, 2/172, 2/197
 1,6-enyne 2/195, 2/197
 enyne metathesis 2/80
 enynes 1/48

- E*-olefin 2/216
 epilachnene 2/444
 epothilone 2/28, 2/115f, 2/298, 2/325, 2/353, 2/356, 2/496
 epothilone A 2/326, 2/356
 epothilone C 2/326, 2/455
 epothilone scaffold 2/328
 epothilone-like 2/328
 epothilones E 2/113
 epoxy resins 2/494
 epoxy-*cis,trans*-diene 2/353
 equilibrium concentration 3/270
Ergot alkaloids 2/345
Escherichia coli 3/216
 ESR 1/191
E-stereochemistry 2/230
E-stilbenes 2/369
E-styrylsilanes 2/468
 ethyl acrylate 2/268
 ethyl crotonate 2/267
 ethyl diazoacetate 1/74
 ethyl vinyl ether 1/115, 1/148f, 1/156, 3/46
 ethyl-3-pentenoate 3/264
 ethylene 2/303
 ethylene gas 2/200
 ethylene polymerization 1/197
 ethylene vinyl acetate 3/343
 ethylene-isobutylene copolymer 3/40
 ethylenolysis 2/280
 ethyridenenorbornene 3/411
 4-ethynyl-1-(octamethylferrocenylethenyl)-benzene 3/232
 eunicellin 2/27
 everninomicin 2/328
 EXAFS 1/192
exo-tricyclo[4.2.1.0_{2,5}]non-3-ene 3/52
 extraction of lanthanide 3/228
E,Z-isomer 2/218
E:Z ratios 2/369
- f**
 farnesol 2/52
 fast mass transfer 3/230
 Feast 3/9, 3/27, 3/36
 Feldheim 3/230
 ferrocenophane 3/127
 [4]ferrocenophane 2/406
 ferrocenylvinylidene 1/101
 fibronectin 3/211
 fine chemical 2/491, 2/506
 Fischer 1/47, 2/177, 3/8, 3/380
 Fischer carbene 2/1, 2/260, 2/404, 3/46
 Fischer carbene complex 1/4, 2/429, 3/277
 Fischer carbyne 1/54
 Fischer chromium-carbene 2/177
 Fischer metal 1/47f
 Fischer-Tropsch 2/494
 Fischer-Tropsch chemistry 1/89
 Fischer-type 1/88
 Fischer-type carbene 1/9, 2/433
 15-F₂-isoprostanes 2/233
 five-coordinate ruthenium 1/68
 fixed stereochemistry 2/30
 flavinoid 2/286
 flow-through reactor 3/250
 fluorenone-doped PFES 3/369
 fluorescent group 3/278
 fluorescent reporter group 2/317
 fluorinated alkoxide 3/287
 fluorinated block copolymers 3/77
 fluoro-alkyl-containing olefin 2/272
 Flynn 3/413
 F_n 3/262
 Fontanille 3/264, 3/275
 Forbes 2/29, 2/338
 formazans 2/67
 Fraser 3/185f
 Fred Tebbe 1/4
 Fu 1/64, 2/338
 Fukuyama 2/345
 Fukuzumi 3/267
 full DFT values 1/163
 fullerene monomer 3/73
 fulvene 3/137
 (–)-fumagillol 2/11
 functional group compatibility 1/124
 functional group tolerance 1/2, 1/80, 2/248
 functionality 3/226
 functionalized cyclooctene 3/53
 functionalized ethylene/vinyl copolymers 1/64
 functionalized polyethylene 3/342
 functionalized polymers 3/45
 furan 3/270
 Fürstner 2/10, 2/49, 2/112, 2/195, 2/199, 2/307f
 Fused bicyclic ring 2/85
 fused ring system 2/164
- g**
 galactose 3/186, 3/216, 3/218ff
 garsubellin A 2/315
 gas phase 1/132, 1/143, 1/160
 gas transport 3/146
 gas-permeable material 3/396
 geissoschizine 2/51
 geldanamycin 2/75, 2/353
gem-dialkyl (Thorpe-Ingold) effect 2/414

- 1,1-geminally-disubstituted diene 2/261
 generation of a conjugated polymer *in situ* 3/123
 geometric isomers 2/344
 Georg 2/113
 Gestwicki 3/205, 3/209, 3/219
 Ghadiri 2/61
 Ghosh 2/11, 2/299, 2/302
 Giardello 1/66
 Gibson 3/26f, 3/189f, 3/193, 3/195, 3/200, 3/278
 Gilliom 3/11
 glabrescol 2/283
 glass transition temperatures (T_g) 3/256
 glucose 3/184ff
 glycoconjugate 2/450, 3/187
 glycolipid 2/112, 2/373
 glycoprotein 3/180, 3/187, 3/206, 3/208f, 3/216
 glycoside 2/280
 glycosidic linkage 3/184
 gold nanoparticle 3/230
 gold particle 3/230
 gold surface 3/209
 Gouverneur 2/474
 graft copolymer 3/15
 graft density 3/92
 graft-chain molecular weight 3/92
 grafted metallocarbenes 1/195
 grafting 1/191
 grafting-from technique 3/94
 grafts 3/311
 Granja 2/19
 Green 1/86, 2/420
 Grela 2/377
 GRGDS 2/317, 3/75
 Grigg 2/47
 (–)-griseoviridin 2/75
 group 10 transition metal catalyst 3/384
 group 6 transition metals 3/376
 group 7 metal carbonyl 3/379
 group-transfer polymerization (GTP) 3/88
 Grubbs 2/209, 2/211, 2/224, 2/226, 3/7, 3/9, 3/11, 3/183, 3/185ff, 3/191, 3/211
 Grubbs' catalyst 2/212, 2/216, 3/45f, 3/58
 Grubbs type compound 1/108
 guanacastepene A 2/9
 Guibé 2/53, 2/407
- h**
 α -H abstraction 1/193
 halicholactone 2/21
 halichondrin B 2/163
 halosaline 2/162
 Hammett constant σ_p 1/126
 Hammett ρ value 1/158
 Hammett σ parameters 1/156
 Hammond Postulate 1/158
 Hanessian 2/9
 Hanna 2/18
 Hanson 2/32, 2/386, 2/501, 3/191, 3/413
 Harrity 2/87, 2/232
 Hayashi 2/407, 2/410
 head-head placements of repeat unit 3/93
 head-tail placements of repeat unit 3/93
 head-to-head 2/261
 head-to-head dimer 2/282
 head-to-tail 1/51
 Heck 2/37, 2/47
 Heck coupling 2/298
 Heck cyclization 2/50
 Heck reaction 3/229, 3/235, 3/313
 Heck-Cassar-Sonogashira type 3/359
 Heck-Hagihara coupling 2/394
 Heck-type reaction 2/393, 3/230, 3/240
 Heddrick 3/65
 helianane 2/41
 helical conformation 3/399
 helical poly(phenylacetylene) 3/398
 helical polymer 3/383
 helical polypeptides 2/57
 helical-substituted polyacetylene 3/397
 helices 2/310
 hemilabile 1/98
 hepatitis C virus 2/496
 Heppert 3/19
 1,6-heptadiyne 1/26
 3-heptyne 1/180
 Herrisson 1/8, 1/51
 Herrmann 1/73, 1/95, 1/198
 HETCOR 1/193
 HETCOR solid-state NMR 1/192
 heteroarm star polymer 3/64
 heteroarmed polymacromonomer 3/100
 heteroatom 1/88, 3/370
 heterocouple 2/284
 heterocycle synthesis 2/382
 heterocycles 2/157, 2/340
 N-heterocycles 2/46
 heterocyclic 2/181, 2/474
 N-heterocyclic carbene (NHC) 1/71, 1/123, 1/155, 2/183, 2/221, 2/224, 3/409
 N-heterocyclic carbene catalyst 2/264
 N-heterocyclic carbene ligands 3/60
 heterocyclic triene 2/138
 heterogeneous catalysts 1/173
 heterogenized 1/74
 heterotelechelic 3/255

- 1,4-hexadiene 3/295
 1,5-hexadiene 2/172, 2/193, 3/296, 3/299, 3/300
 2,4-hexadiene 3/312, 3/332
 2,5-hexadiene 3/313
 1,3,5-hexatriene 3/312
 3-hexene 1/50, 2/492
 5-hexenylchlorodimethylsilane 2/485
 Hg(CCl₃)₂ 1/92
 high (8:1) *Z:E* selectivity 2/309
 high catalyst commitment 1/155
 high oxidation state 1/13
 high oxidation state alkylidene complexes 1/9
 high-capacity anion exchange support 3/227
 higher oxidation state early metal complexes 2/1
 highly alternating microstructure 3/343
 highly functionalized reagents 2/269
 highly potent analogues 2/307
 high-throughput processes 1/76
 high-throughput screening 3/235
 Hillmyer 1/64, 3/268, 3/271
 H₂IMes 1/127
 Hirama 2/43, 2/45
 Hitachi Chemical 3/410
 HIV 2/501
 homoallylic 2/473
 homoallylic substrate 2/267
 homobimetallic ruthenium 3/59
 homocoupled 2/250
 homodimerization 2/262, 2/330
 homodimers 2/251, 2/369
 homogeneous olefin metathesis catalysts 2/249
 homologation 2/250
 homometathesis 2/133
 homopolymer 3/62
 Horner-Emmons macrocyclic 2/299
 Horner-Emmons reaction 2/379
 Horner-Wadsworth-Emmons 2/268
 Hoveyda 2/73, 2/88, 2/224, 2/228, 2/377
 Hsung 2/83
 hydrazine 2/384
 hydrido carbyne isomer 1/147
 hydrido(vinylidene) complexes 1/100
 hydrindane 2/90
 hydroazulenes 2/153
 α hydrogen abstraction 1/12, 1/19
 hydrogenated 2/163, 2/385, 2/415
 hydrogenation 3/149, 3/271, 3/274, 3/338
 hydrogenation catalyst 2/505
 hydrogenation of ROMP polymers 3/413
 hydroindene 2/153
 hypodentals 2/153
 hydrophilic polymer 3/79
 hydroquinone polymers, conjugated 3/138
 hydroxy alkenes 2/472
 hydroxyl *E*-stilbenoids 2/369
 hydroxylamine hemiketal 2/305
N-hydroxysuccinimide 2/380f, 2/388
 hydroxytelechelic polybutadiene (HTPBD) 3/74
 hydroxy-terminated polymer 3/258
 hyperpolarizability 3/155

i
 IBM 3/413
 Ibrahim 2/67
 Ichikawa 3/267
 ICP-OES 3/241, 3/245
 ill-defined 3/284, 3/286
 imidazolium ligand 2/146
 imidazoylidene-based 2/249
 imido alkylidene 1/15
 imido and alkoxide moieties 2/129
 imido family 1/42
 imido ligand 1/19
 imido tungsten-alkylidene 3/19
 imine dissociation 1/122
 immobilized 3/237
 immobilized ligand 3/230
 imprinting 2/109
 indole alkaloids 2/309
 indolizidine 2/158, 2/162
 indomethacin 3/196
 induction period 3/335
 inductively coupled plasma-optical emission spectroscopy (ICP-OES) 3/237
 infusion 3/410
 ingenol 2/26, 2/303
 inhibitor 3/204f, 3/208, 3/211, 3/216, 3/220
 initiation efficiency 3/380, 3/387
 inorganic support 2/477
 insect pheromone 2/491f
 insertion mechanism 3/377, 3/382, 3/389
 inside-outside 2/26
 inside-outside tricyclic ring 2/19
in situ catalyst 3/354, 3/360, 3/362, 3/370
in situ formation 1/67, 1/73
in situ Mo catalysts 2/143
in situ polymerization 2/386
 integrin 3/211
 integrin-protein interaction 3/74
 interchange reactions 3/291
 interlocked 32-, 38-, and 32-membered rings 2/410
 14e-intermediate 1/129
 intermolecular 2/161

intermolecular decomposition 1/15
 intramolecular hydrogen bond 3/399
 intramolecular π complex 1/149
 iodide 1/144
 ion chromatography 3/240
 ionic liquid 3/383
 Iqbal 2/60
 ircinal 2/116
 Ireland-Claisen rearrangement 2/501
 iridium-based catalyst 2/208
 iron 1/81
 iron-based heterogeneous Ziegler-type catalyst 3/384
 iron-complexed conjugated 2/76
 isocyanide 1/86
 isomerization 2/27
 isoprostane 2/233
 isotactic 3/28
 isotactic poly(propylene) 3/166
 isotactic polymer 3/152
 isotope effects 1/158
 Ivan 1/6, 3/9, 3/18, 3/152
 Ivoclar Vivadent 3/413

j

Janus-type shape 3/98
 Jenkins 2/17
 Johnson 1/62
 jojoba oil 2/492
 Julia-Kocienski 2/299

k

Katz 1/173, 2/177, 2/207, 2/432, 3/7f
 Katzenellenbogen 2/58
 Kawai 2/410, 3/295, 3/316
 Kazmaier 2/58
 Kerr Corporation 3/413
 Kessler 2/64
 η^2 -ketene 1/89
 Kevlar 3/238
 Khosravi 3/27
 k_i/k_p 3/22
 Kiessling 1/74, 2/317, 3/184, 3/187, 3/198, 3/200, 3/204, 3/207, 3/217f, 3/278, 3/413
 kinetic analysis 3/332
 kinetic control 2/254
 kinetic experiments 3/333
 kinetic isotope effects 1/158
 kinetic product 2/334
 kinetic resolution 1/26, 1/65, 2/94, 2/129, 2/475
 knots 2/98
 Kobayashi 2/377
 Kosan Biosciences 2/497

Koskinen 2/22
 Kozmin 2/185
 k_p/k_i 3/22
 Krafft 2/19, 2/304
 Kraton 3/330
 Kress-Osborn 1/35

l

Labreque 2/306
 lactam 2/52f, 2/219, 2/368
 β -lactam 2/198
 γ -lactam 2/154
 lactamization 2/238
 Lamaty 2/59
 Lambert 2/420
 Langer 2/23
 Langmuir films 2/276
 lanthanide 3/240
 Lappert 1/80, 1/87
 largest molecule 2/45
 laulimalide 2/298
 (–)-laulimalide 2/11
 Lautens 2/95
 lead tetraacetate 2/18
 Lebreton 2/48
 lectin 3/203f, 3/206
 Leigh 2/100
 Lemal 1/80
 leukemia 2/307
 Lewis acid co-catalysts 1/48
 Lewis acid sites 1/197
 Lewis acidic 3/267
 Lewis acids 1/36, 1/53
 Lewis base 3/267
 Lewis-acid co-catalyst 2/299
 Lewis-acid-free 3/297
 libraries 2/22, 2/107, 2/326, 2/361, 2/364, 2/372f, 2/377
 libraries of polyurethanes 3/256
 library of macrocycles 2/241, 2/244
 library of monomers 3/258
 library synthesis 2/362
 Licandro 2/420
 ligand rotation 1/167
 light-initiated cross-linking 2/482
 Linderman 3/230
 Lindlar hydrogenation 2/438
 Lindlar reduction 2/440, 2/450f, 2/454
 Lindlar-type reduction 2/443, 2/459
 linear 3/36
 Linear ethylene/acrylate ester copolymer 3/343
 linear polyethylene 3/338f
 liquid crystalline (LC) microphase 3/80

- liquid crystalline behavior 3/146
- liverwort diterpene 2/16
- living 1/25
- living anionic 3/92
- living character 3/245
- living metathesis 3/52
- living polymer 3/2, 3/231
- living polymerization 1/6, 1/43, 3/2, 3/4, 3/19, 3/26, 3/36, 3/48, 3/53, 3/182, 3/226, 3/260, 3/284, 3/384
- living ROMP 3/16, 3/21f, 3/22, 3/24, 3/26f, 3/35f, 3/46, 3/57ff, 3/64
- longithorone 2/199
- (-)-longithorone 2/312
- Lord Corporation 3/411
- Lovely 2/410
- low concentrations 2/7
- low oxygen permeability 3/412
- L-selectin 2/317
- luminescent property of conjugated polymer 3/400
- Luning 2/66
- Lyondell 3/408
- lysergic acid 2/346

- m**
- [M]_c 3/270
- Maarseveen 2/53
- macrocarbocycle 2/238
- macrocyclic 2/106, 2/112
- macrocyclic ketones 2/243
- macrocyclic lactones 2/5
- macrocyclic peptide helices 2/311
- macrocyclization 1/65, 2/6, 2/66, 2/70, 2/96, 2/238
- macroinitiator 3/88, 3/266, 3/274
- macrolactone 2/238
- macrolactonization 2/238
- magic ring formation 2/99
- magnetization transfer 1/114
- main group metal functionality 3/82
- Maleczka 2/310
- mannose 3/184, 3/186, 3/198, 3/204, 3/206
- Manzamine A 2/116, 2/118, 2/342
- Marco-Contelles 2/10
- Markov distribution 3/310
- Martin 2/309
- Materia 3/410, 3/412
- material chemistry 2/275
- matrix-assisted laser desorption (MALDI) 1/135
- Matyjaszewsky 3/227
- McMurry 2/338
- M–C_x bond lengths 1/17
- meadowfoam oil 2/493
- mechanism 2/162, 3/47
- mechanistic insight 3/357
- mechanistic proof 3/355
- mechanistic studies 2/131
- medium-ring unsaturated amines 2/136
- medium-sized 2/32
- medium-sized carbocycles 2/16
- Mehta 2/9, 2/29
- melting point 3/145, 3/298, 3/338
- 11-membered cycloalkyne 2/446
- 82-membered knotted ring 2/103
- 15-membered macrocycle 2/414
- 17-membered macrocycle 2/415
- 14-membered macrolides 2/496
- 15-membered macrolides 2/496
- 5-, 6-, and 7-membered monocyclic systems 2/338
- 8-membered ring 2/30, 2/40, 2/75, 2/155, 2/304, 2/342
- 11-membered ring 2/332, 2/334
- 12-membered ring 2/306, 2/354
- 13-membered ring 2/308, 2/316, 2/343
- 14-membered ring 2/355
- 20-membered ring 2/310
- 7-membered sulfonamide analogues 2/504
- Merck 2/501
- Merck Sharp & Dohme 2/504
- mercury(II) 3/229
- MeReO₃/SiO₂–Al₂O₃ 1/198
- Merrifield resin 2/369, 2/371
- meso-bicyclic product 2/134
- mesogenic norbornene derivative 3/80
- mesomorphic behavior 3/81
- mesomorphism 3/81
- metal carbene 3/377, 3/385
- metal carbene catalyst 3/378
- metal carbonyl catalyst 3/379
- metal carbonyl-based catalyst 3/378
- metal halide-based catalyst 3/378, 3/385
- metal halide-based living polymerization catalyst 3/385
- metal hydrides 1/127
- metal-carbon double bonds 2/1
- metal-containing monomer 3/388
- metal-containing substrate 2/403
- metallacarbene-olefin complex 3/164
- metallacycle 1/22
- metallacyclobutadiene 1/173, 1/177, 2/433, 3/355
- metallacyclobutadiene intermediate 3/357
- metallacyclobutane 1/5, 1/13, 1/18, 1/42, 1/113, 1/160, 1/163, 2/168, 3/7, 3/9, 3/294

- metallacyclobutene 1/4, 1/56
- metallacyclohexatriene 1/178
- metallacyclopentadiene 3/355f, 3/356
- metallacyclopentane 1/42
- metallaocene catalyst 3/173
- metallocarbene 1/44
- metallocene catalyst 3/344
- metallocene-containing monomer 3/388
- metallocyclobutane 2/280
- metallocyclobutane intermediates 2/207
- metalloproteinase enzymes 2/500
- metal-templated RCM 2/96
- MetatheneTM 3/410
- metathesis degradation 3/329
- metathesis mechanism 3/377
- metathesis of internal alkynes 1/186
- metathesis-based cyclorelease 2/328
- methacrylate group 3/110
- methacrylate polymer 3/110
- methanol 1/127
- methyl acrylate 1/106, 3/318
- 2-methyl-2-butene 3/308
- methyl dec-9-enoate 1/53
- methyl 5-eicosenoate 2/493
- 3-methyl-1,5-hexadiene 3/302, 3/305
- 7-methylnorbornadiene 3/158
- 1-methylnorbornene 3/168
- 2-methylnorbornene 1/51
- 7-methylnorbornene 3/172
- 3-methyl 1,4-pentadiene 3/300
- methyl oleate 1/190, 1/198, 2/494
- methylene carbene 1/56
- methylene complex 1/17
- α -methylene- γ -lactone 2/18
- 2-methyl-1,5-hexadiene 3/307
- methylidene 1/119
- methylidyne complexes 1/183
- N-methylmaleimide 2/172
- Metton 3/408
- Meyers 2/16, 2/75
- M–H bond 2/465
- Michaelis-Arbuzov reaction 2/270
- microelectronic application 3/65
- microencapsulated DCPD 3/411
- microglobule 3/244f, 3/247
- microphase-separated morphology 3/80
- microphase-separated region 3/82
- microporosity 3/247
- micro-separation 3/241
- microstructural 3/143
- microstructure 3/144f
- microwave 2/450
- microwave heating 2/435
- microwave irradiation 3/355
- migraine 2/503
- migratory insertion 2/465
- miktoarm star polymer 3/64
- Milstein 1/67
- Mirkin 2/406
- mitomycins 2/344
- Mitsunobu products 2/388
- Mitsunobu reaction 2/386
- MM2 calculations 2/24
- Mo-based complexes 2/129
- Mo-carbene catalyst 3/387
- Mo-catalyzed AROM 2/130, 2/133
- Mo-catalyzed AROM/CM 2/142
- Mo(CO)₆ 2/432
- Moeller 2/53
- Mol 2/375
- molecular assemblies 2/105
- molecular knot 2/102
- molecular machines or motors 2/105
- molecular wire 3/129
- molybdacyclobutadiene 1/180
- molybdacyclobutane 1/19, 1/23f, 3/21, 3/286, 3/302
- molybdenum 1/19
- molybdenum alkylidene 2/264
- molybdenum hexacarbonyl 1/173
- molybdenum neopentylidyne complexes 1/180
- molybdenum-based 2/260
- molybdenum-based catalyst 3/354
- molybdenumhexafluoroneophylidene-(dimethylimido) 3/75
- monocillin 2/353
- monocillin I 2/355
- monodentate 1/120
- monodispersed linear polyethylene 3/78
- monofunctional N-alkyldicarboxyimidonorbornenes, termed CnM 3/107
- monolayer 3/146
- monomers 3/131
- monomer-to-chain-transfer agent 3/273
- mononorbornenyl telechelic polyphosphazene 3/95
- monosaccharide 3/187, 3/205
- monosubstituted acetylene 3/378
- monotelechelic 3/255
- Monte Carlo simulations 1/137
- Moody 2/49
- Mori 2/81, 2/180, 2/198
- morphine 2/504
- Mortreux 1/186, 2/77, 2/432
- Mortreux catalysts 2/434
- Mortreux system 2/437
- Mosher amide 2/381

- mosquito oviposition pheromone (MOP) 2/493
 motuporamine C 2/444
 m and r stereochemistry 3/151
 Mülhaupt 3/187
 Mulliken population 1/161
 multidentate ligands 1/70
 multifilament fiber 3/238
 multivalent drug 3/413
 multivalent ligand 3/180f, 3/183, 3/203ff, 3/209, 3/211, 3/216, 3/218
 Mulzer 2/299
 Murai 2/180, 2/194
 (R)-(-)-muscone 2/506
 myo-inositol 2/15
- n**
- nakadomarin A 2/446
 Nakagawa 2/15, 2/73
 nanoclusters 3/82
 nanoparticles 2/406
 naphthalene-derived 2/161
 Natta 3/6
 natural product synthesis 2/284
 natural rubber elastomer 3/240
 nature 2/151
 Nb and Ta 3/381
 NBE-derivatized silica 3/232
 N-containing unsaturated heterocycles 2/135
 nebevivolol 2/157
 Nelson 2/11
 NeobiopolymerTM 3/413
 Neogenesis Pharmaceuticals 3/413
 neoglycopolymers 2/317
 neopentyl ligand 1/11, 1/175
 neopentylidene 1/22
 neopentylidene ligand 1/176
 neopentylidyne 1/176, 1/184
 neutral and cationic rhodium carbenes 1/97
 Nguyen 2/406, 3/194, 3/196, 3/230
 Nicolaou 2/3, 2/113, 2/115f, 2/368, 2/373, 2/497
 Nielsen 2/33
 Ni-mediated[4+4]cycloaddition 2/304
 nitrile rubber 3/414
 nitriles 1/180
 nitrogen heterocycles 2/350
 NK-1 receptor antagonist 2/501
 NMR spectral patterns 3/389
 NMR spectroscopy 3/147, 3/332
 Nolan 1/73, 2/375
 nonlinear architecture 3/98
 nonlinear optical effect 3/120
 nonlinear optical material 2/276
- non-racemic organic molecules 2/128
 nor-1,6-germacradien-5-ol 2/21
 norbornene 1/52, 1/158, 2/152, 2/154, 2/188, 2/476, 2/478, 3/408
 norbornene-cyclobutene diblock copolymer 3/78
 norbornene-cyclobutene triblock copolymer 3/78
 norbornene-terminated macromonomer 3/98
 norbornene-tethered pincer 2/420
 norbornenyl-substituted thiophene 3/112
 norbornyl 2/218
 norbornyl ROCM 2/221
 Norsorex[®] 3/408
 North 3/26, 2/169, 3/195
 Novak–Grubbs 1/63
 novel platform structures 2/491
 Nubel 3/267
 nucleic acid bases 3/220
 nucleic acid hybridization 3/195
 nucleobase 3/193
 nucleophilic 1/62
 nucleophilic alkylidene 1/13
 nucleotides 2/280
 number average functionality (F_n) 3/259
 nylon 3/238
- o**
- OCMe(CF₃)₂ ligand 1/19
 1,4-octadiene 3/295
 1,7-octadiene 3/241
 1,9-octadiene 2/470
 octalactin A 2/19
 2,4,6-octatriene 3/312
 Ogasawara 2/407, 2/410
 Ojima 2/28
 Okada 3/278
 α -olefin 2/247
 olefin cross-metathesis (CM) 2/246
 olefin isomerization 2/93, 2/261
 olefin metathesis 1/6
 olefin metathesis polymerization 3/4
 olefin polymerization 3/87
 olefination methods 2/247
 olefinic precursors 2/250
 oleic acid 2/494
 oleic acid derivatives 2/373
 oleochemical sources 2/250
 oligomerization 1/180
 oligonucleotide 3/194, 3/250
 oligopeptide 3/191
 oligosaccharide 2/328, 2/368, 2/372
 OLR pheromone 2/492
 omnivorous leafroller 2/492

- one-step metathesis reaction 1/159
- optical properties 2/478
- optically active 3/152
- optically enriched compounds 2/138
- optoelectronic properties 2/469
- ordering of polyacetylene 3/133
- OrganoCatalystTM 2/495
- organometallic and anthracene-containing 3/365
- organometallic co-catalyst 3/378
- orthogonal method 2/272
- orthometallation 1/87
- Osborn 1/6, 1/14, 1/22, 1/35, 1/184, 3/9, 3/18
- osmium complex 1/105
- osteoporosis 2/306
- Otton 3/264
- Overman 2/27
- 7-oxanorbornadiene 3/24
- 7-oxanorborn-2-enedicarboxylic anhydride 3/248
- 7-oxanorbornyl derivatives 2/218
- oxazole library 2/384
- oxazoles 2/382
- oxidative addition 1/117
- oxidative cleavage 2/472
- oxidative cyclization 2/467
- oxidative polymer reaction 3/401
- oxidative polymerization of thiophene 3/112
- oxo ligand 1/14, 1/175
- oxo-free alkylidene 1/14
- oxonorbornene 1/74
- oxophilicity 1/62
- oxygenated diterpene 2/303
- Ozawa 1/101, 3/277
- ozone 2/394
- P**
- paclitaxel 2/454
- PAEs 3/365
- pair-wise metathesis mechanism 2/206
- Paley 2/420
- palladium 2/177
- palladium(II) 3/229
- palladium-catalyzed enyne 2/178
- palm tree-like copolymer 3/101
- Pandit 2/51
- Paquette 2/18, 2/75f, 2/112
- [7,7]-paracyclophane 2/314
- [2,2]paracyclophane-1,9-diene 3/126
- paracyclophan-1-ene 3/43
- parallel synthesis 2/377
- paramagnetic metalloporphyrin 3/401
- para*-substituted triphenylphosphine 1/126
- Parshall 2/209
- patents 2/491
- Paterson 2/299, 2/302
- Pattenden 2/310
- pattern construction 3/132
- Pauson-Khand cyclization 2/43
- PCy₃ 1/117
- Pd-catalyzed 3/359
- Pd-catalyzed reactions 2/151
- Pd-mediated 2/310
- peach twig borer 2/492
- peduncularine 2/349
- Peierls distortion 3/119
- pendant polar functional groups 3/76
- penicillin 3/196
- pent-4-enyl acetate 1/53
- Pentam 3/408
- pentyl vinyl ketone 2/233
- peptide 3/61, 3/191
- peptide isosteres 2/446
- peptide-containing monomer 3/345
- peptide-substituted polymer 3/189
- peptidomimetics 2/278, 2/368
- permeability 2/484
- Petasis 2/3
- petrochemical 3/407
- petrochemical sources 2/250
- PF-based light-emitting diode 3/369
- Pfizer 2/503
- PF's optical and emissive behavior 3/365
- PGE analogues 2/453
- Ph₃SiOH 2/435
- pharmaceuticals 2/491, 2/506
- phase-transfer reagent 2/330
- PhCHN₂ 1/96
- phenanthroline 2/99
- 1,10-phenanthroline 2/66
- phenol 2/432, 3/355
- phenylacetylene 1/53, 1/55, 1/99, 1/101, 3/156
- phenyldiazomethane 1/65
- N-phenyl-di-3-butenylamine 3/319
- phenyltolylacetylene 1/181
- Philips catalysts 1/197
- Phillips 2/90
- Phillips triolefin process 3/407
- phosphine dissociation 1/113, 1/115, 1/118
- phosphine donor 3/82
- phosphine exchange 1/114
- phosphine exchange rates 1/124
- phosphine ligands 3/47
- phosphine re-coordination 1/116
- phosphines 2/274
- phosphonate 2/270

- phosphor-heterocycles 2/32
 photochemical 1/44, 3/318
 photoconductivity of poly(phenylacetylene) 3/400
 photolithography 3/132
 photoluminescence 2/480
 photoluminescence efficiency 3/128
 photo-responsive liquid crystalline polyacetylene 3/400
 PHSRN 2/317, 3/61
 physisorbed 3/240
 Pinazzi 2/208
 pincer complexes 2/420
 pipercolinates 2/368
 piperidine 2/159, 2/192
 PiPr_3 1/98
 Piscio 2/62, 2/474
 pK_a 1/126
 plastic electronics 3/132
 platinum-catalyzed 2/194
 Plumet 2/154
 PNE 3/365
 P_{O_2} values 3/396
 polarity 3/77
 polarized 1/10
 1,2-polybutadiene 2/86
 poly(1,4-phenylenevinylene) (PPV) 3/38
 poly(3-methylbutylene) 3/302
 poly(5,6-bis(trifluoromethyl)norbornadiene) 3/160
 poly(anthracenylene vinylene) 3/135
 poly(arylenevinylene)s 3/126
 poly(aryleneethynylene) 3/377
 poly(aryleneethynylene)s (PAEs) 3/354
 poly(aryleneethynylene)s (PCE) 3/370
 poly(BTFMND) 3/84
 poly(cyclodecene) 3/158
 poly(cyclododecene) 3/158
 poly(cyclopentene) 3/158
 poly(cyclopentenylenevinylene) 2/484
 Poly(diphenylacetylenes) 3/397
 poly(DPA) 3/381
 poly(*N*-(norbornene-5-carboxyl)- β -cyclodextrin ester) 3/231
 poly(naphthylene vinylene) 3/135
 poly(norbornene) 3/148, 3/157f
 poly(*paraphenyleneethynylene*) 3/358
 poly(phenylacetylene) 1/53, 3/400
 poly(phenylene ethynylene) 3/128
 poly(*p*-phenylenevinylene) 3/44, 3/86
 poly(TMSP) 3/381, 3/396
 poly[(didodecyl)fluorenyleneethynylene]s (PFE) 3/368
 polyacetoxy δ -lactone 2/302
 polyacetylene 3/37, 3/119, 3/311f, 3/375
 polyalkenamers 1/49
 polyamine 3/319
 polybutadiene 3/267, 3/330f
 polycarbonate 3/323
 polycarbosilanes 2/478, 2/481
 polycondensation 2/479
 polycyclic ether 2/3, 2/38, 2/43
 polycyclization 2/164
 poly-DCPD 3/409
 polydispersity 3/16, 3/20
 polydispersity index (PDI) 3/291
 polyene 3/312
 polyene oligomers capped by *t*-butyl groups 3/133
 polyether polyol 3/257
 polyethylene 3/36, 3/43, 3/332, 3/341, 3/344
 polyfluorene (PF) 3/365
 polyhydroxylated 2/302
 polyisoprene 3/331
 polyisoprene-aldehyde (PIA) 3/83
 polymacromonomer 3/98
 polymer 3/399
 polymer additives 2/491
 polymer latex 3/54
 polymer stereochemistry 3/27, 3/31
 polymer/drug conjugate 3/196
 polymer/oligonucleotide hybrid 3/194
 polymer-bound 2/375
 polymer-bound olefins 2/256
 polymeric ligand 3/181, 3/199, 3/209
 polymeric scaffold 3/180
 polymeric support 2/256
 polymerization 1/180
 polymerization of acetylene 3/375
 polymerization of terminal alkynes 1/183
 polymerization solvent 3/385
 polymerizations of diacetylene 3/128
 polymer-supported 2/471
 polymer-supported chiral Mo catalyst 2/143
 polymer-supported synthesis 2/191
 polynorbornene 3/330
 polyoctynamer 3/357
 polyoligomeric silsesquioxane (POSS) 1/191
 polypentenamer 3/408
 polypeptide 3/180
 polyphenylenevinylene (PPV) 3/313
 poly-*p*-phenylene-vinylene 2/480
 polyribose 3/187
 polystyrene graft 3/92
 polystyrene resin 2/191
 polystyrene-aldehyde (PSA) 3/83
 poly-*trans*-isoprene 3/330
 polyurethane 3/255

- polyvinylpyridine 2/384
 - poly- α -olefin-polynorbornene copolymer 3/87
 - pore-size distribution 3/250
 - porogenic 3/242f
 - porogens 3/4, 3/245
 - Porri 1/104
 - Postema 2/31
 - post-polymerization modification (PPM)
 - 3/181, 3/183, 3/197
 - PPE-PPV copolymer (PPEV) 3/363
 - PPEs 3/360
 - PPNE 3/365
 - PPV derivative 3/136
 - PPVs 3/360
 - practicality 2/143
 - pre-activated 3/357
 - pre-activated catalyst 3/362
 - pre-column 3/228
 - precursor 3/122
 - precursor polymer, dehydrogenating 3/134
 - prenyl group 2/263
 - probe 3/199
 - producing ABA-type block copolymer 3/5
 - producing AB-type block copolymer 3/5
 - product-selective 2/251
 - propagating species 1/126, 1/128
 - propargyl acetate 2/192
 - propargyl halides 1/66
 - propargylic 2/190
 - propargylic alcohol 2/193, 2/371
 - propargylic amines 2/169
 - propargyloxy 2/188
 - propionic ester 3/398
 - propylene 2/267
 - propylidene 1/118
 - propylidene complex 1/146
 - propyne 1/54
 - propynylbenzene 3/355
 - prostaglandin E₂ 2/440
 - prostaglandin E₂-1,15-lactone 2/79, 2/450
 - protected olefinic linker 2/372
 - N-protected 3-pyrrolines 2/495
 - protecting group 2/159
 - protein 3/274
 - protein-carbohydrate interaction 3/203, 3/206
 - protein-lipid bilayer 3/275
 - protodesilylation 2/472
 - α proton 1/20f
 - β proton 1/183
 - Prunet 2/18
 - pseudorotaxane 2/101
 - pseudo-Wittig 1/192, 1/195
 - pulsed addition 3/279
 - purified 2/364
 - pyroglutamic acid 2/81, 2/198
 - pyrrole moiety 2/308
 - pyrrolidine 2/185f
 - pyrrolidinoazocine 2/339
 - 3-pyrrolines 2/494
 - 4-pyrones 2/221
- q**
- QM/MM calculations 1/151, 1/165
 - QM/MM hybrid method 1/160
 - quadrupole mass filter 1/136
 - quinoline 2/15
 - quinolizidine 2/158
 - quinone 3/138
 - Quintessence Biosciences 3/413
- r**
- radical 3/4
 - radicol 2/75, 2/353
 - radicol-like macrolides 2/353
 - radulanin 2/41
 - Raman spectroscopy 3/147
 - random copolymer 3/72, 3/226
 - rare earth elements 3/240
 - ratio of E- to Z-11-tetradecenyl acetate 2/492
 - Rawal 2/50
 - RC=Cme 1/176
 - RCAM 2/454
 - RCM 1/132, 1/156, 3/293
 - RCM olefin-isomerization 2/505
 - RCM-ROM-RCM 2/160
 - Re₂O₇/Al₂O₃ 1/190, 1/197
 - reaction coordinate 1/161
 - reaction injection molding (RIM) 1/1, 3/105, 3/256
 - reactivity ratio 3/72
 - receptor 2/57
 - receptor clustering 3/206, 3/219f, 3/220
 - recyclability 1/76f
 - recyclable 1/123, 1/129
 - recyclable chiral ruthenium catalyst 2/230
 - recycled 2/492
 - recycling 3/329, 3/414
 - redox modification 3/120
 - regio- and stereoselective ROCM 2/216
 - regioisomer 2/215
 - regioselectivity 2/215
 - regiospecificity 1/48, 2/271
 - Reitz 2/56
 - relay 2/164
 - remote stereocontrol 2/252
 - removable tethers 2/252
 - Renaud 2/37, 2/81

- repetitive ROMP reaction 3/96
- reporter group 3/199, 3/209, 3/220
- resin transfer molding (RTM) 3/105
- resin-bound allylsilane 2/271
- resin-capture 2/222
- resting state 1/154
- resting-state metal carbene 2/257
- retention of configuration 1/199
- retrocycloaddition 2/207
- Reyx 3/264
- RGD 3/61, 3/74
- Rh catalyst 3/382, 3/399
- Rh complex 3/385
- Rh-catalyzed living polymerization 3/388
- rhenacyclobutadiene 1/185f
- rhenium 1/20
- Rh-H complex 3/389
- rhynchophylline 2/347
- ribonucleic acid (RNA) 3/193
- ribose 3/186
- Richards 2/407
- Riera 2/48
- rigid alkenyl C–C bond construction 2/290
- rigid rods 3/241
- ring chelate 3/50
- ring expansion 2/226
- ring rearrangement metatheses (RRM) 2/152
- ring-closing metathesis (RCM) 2/128
- ring-opening cross-metatheses (ROCM) 2/205, 2/211
- ring-opening insertion metathesis polymerization (ROIMP) 3/103
- ring-opening metathesis polymerization (ROMP) 3/72
- ring-opening olefin metathesis polymerization (ROMP) 3/6
- ring-opening polymerization of norbornene 3/380
- ring-substituted phenylacetylene 3/388
- Rink resin 2/371
- Ripka 2/58
- (–)-roccellaric acid 2/284
- ROCM 2/218
- ROCM in Total Synthesis 2/230
- ROCM/CM reaction sequence 2/224
- ROCM/Cope rearrangement strategy 2/232
- ROCM/olefination reaction 2/211
- ROM copolymerization 3/100
- ROM/RCM 2/186f, 2/377
- Romo 2/316
- ROMP 1/35, 1/132, 3/1, 3/7, 3/11, 3/13ff, 3/20, 3/181, 3/258, 3/288
- ROMP initiator 3/72
- ROMP monoliths 3/413
- ROMP of cyclic olefins 1/105
- ROMP/CT 3/260
- ROMPgel 2/378f, 3/230, 3/413
- ROMPspheres 2/391
- Rooney 3/9, 3/152
- Roper 1/62, 1/68, 1/95, 1/108
- roseophilin 2/27, 2/199, 2/308
- rotamer 3/167
- rotation 1/21
- rotation of the PCy₃ ligand 1/166
- rotaxane 2/97f
- Roy 2/171
- Ru catalysts 2/145
- [RuCl₂(η⁴-C₈H₁₂)]_x 1/98
- Ru(H₂O)₆(Tos)₂ 1/63, 3/45
- rubber/plastic material 3/411
- Rudler 2/404
- Rudler carbene 3/380
- Ru-H 1/86
- Ru-mediated 2/310
- ruthenacycle 2/183
- ruthenium methylidene 1/118
- ruthenium-based catalyst 2/249
- ruthenium-carbene complex containing an activated carbon-halogen bond 3/90
- ruthenium-catalyzed *trans*-selective hydrosilylation 2/456
- ruthenium-ethoxycarbene complex 3/94
- ruthenium-hydride 2/93
- Rutjes 2/407
- s**
- saccharide 3/184, 3/187, 3/203f, 3/208
- Sakurai reaction 2/252
- salicylhalamide 2/71, 2/113, 2/306
- salicylhalamides A and B 2/505
- Sanders 2/99
- sanglifehrin A 2/74
- Sarkar 2/420
- Sasol 2/494
- Sauvage 2/98, 2/102, 2/106, 2/410
- scavenger 2/386
- scavenging 2/388
- SCF-X α -SW calculations 1/24
- Sch 38516 (fluvirucin B1) 2/73
- Schiff bases 1/70
- Schinzer 2/115, 2/497
- Schmidbaur 1/10
- Schmidt reaction 2/349
- Schottky barrier-type solar cells 2/484
- Schreiber 2/112, 2/365, 2/369
- Schrock 2/1, 2/228, 2/260, 2/405, 3/8, 3/16, 3/19, 3/27, 3/63, 3/186, 3/199
- Schrock alkylidyne 2/434

- Schrock carbene 3/380
Schrock carbyne complexes 3/354, 3/359
Schrock catalyst 2/212, 3/21
Schrock-type 1/62
screening 1/27
sealant 3/326
second prenyl moiety 2/315
secondary isotope effects 1/156, 1/161
secondary metathesis 2/71, 2/251, 3/17,
3/26, 3/48, 3/53, 3/60, 3/77, 3/126, 3/158,
3/298
secondary metathesis reactions 3/46
securinine 2/503
selectin 3/206, 3/209
selectin-ligand interaction 3/207ff
selective ring-opening olefination process
2/210
selective ROCM 2/207, 2/217
self-healing 1/77
self-healing polymer 3/411
semi-telechelic 3/278
semi-telechelic polynorbornene 3/277
separation media 3/232
separation science 3/251
Sepracor 2/501
sequence-specific copolymer 3/338
sequential living polymerization 3/387
sequential ROCM 2/226
sequestered nanoclusters 3/82
sesquiterpene lactone 2/303
seven coordinate Mo(II) compound 3/380
seven coordinate W(II) compound 3/380
Shair 2/199, 2/312
Shell Higher Olefins Process (SHOP) 3/408
Shibasaki 2/15
SHOP process 1/1
short-chain branch distribution (SCBD)
3/340
Shultz 2/320
Si-allyl 3/237
side groups onto polyacetylene 3/376
side-chain liquid crystalline polymer 3/80
sigma-donor 1/126
silacyclopent-3-ene 2/473
silacyclopentane 2/485
silaketals 2/473
silanol 1/193, 3/355
silica 1/192
silica-supported 1/198
silicon tether 2/31
silicon-containing block copolymer 3/78
silicon-containing end-functionalized polymer
3/78
silicon-containing homopolymer 3/78
silicon-heterocycles 2/29
silicon-tethered 2/30, 2/472
siloxo triene 2/133
siloxoalkyne-alkene 2/185
silver 1/87
single-component carbene catalyst 3/380
single-component transition-metal catalysts
2/248
Sinn 2/1
size exclusion chromatography 3/244
skeletal reorganization 2/176
slow-release 1/77
Smith 2/109, 2/306, 2/314
Snapper 2/93, 2/304, 2/476, 3/300
Snieckus 2/40
solar cells 3/125
sol-gel 2/476, 3/242
sol-gel-supported catalyst 2/377
solid bead 2/361
solid-phase 2/65, 2/112
solid support 2/64, 2/361
solid-phase RCM 2/62
solid-phase resins 2/378
solid-phase supports 2/390
solid-phase synthesis 2/116
solid-phase transformations 2/221
solid-state defect 3/369
solid-state NMR 1/191, 3/147
solid-support-bound 2/62
solid-supported 1/74
solubility in methanol 1/122
soluble chiral polyacetylene 3/125
soluble polymer 3/233
solution-phase behavior 1/167
SOMC 1/201, 1/191
Sonogashira-Hagihara coupling 2/394
Sonogashira-Hagihara reaction 3/229
Sonogashira-Hagihara-type reaction 3/230
Speckamp 2/349
Spessard 2/315
sphere-type shape 3/98
Spirocyclic butenolides 2/23
spirocyclic pyrans 2/22
spiro-cyclopentene 2/334
Spitzner 2/23
split-and-pool combinatorial synthesis 2/326
split-pool syntheses 2/112
(\pm)-sporocholnol 2/232
SRN 3/75
star-shaped block copolymer 3/101
star-shaped macromolecule 3/102
star-shaped polymers 3/384
star-shaped polymer structure 3/4
star-shaped polymers via ROMP 3/63

- stationary phase 3/231
- statistical distribution 2/256
- statistical product distributions 2/288
- statistical ratio 2/258
- Staudinger reaction 2/386
- stemoamide 2/198
- (-)-stemoamide 2/81
- stereochemical outcome 2/307
- stereochemical relay 2/255
- stereocontrol 2/326
- stereogenic at the metal center 2/146
- stereoisomerization 3/145
- stereoregular polymers 3/27, 3/29
- stereoselective addition 2/348
- stereoselective ROMP 3/85
- stereoselectivity 1/45, 2/70, 2/73, 2/252, 3/145
- stereospecific polymerization 3/384
- stereospecificity 1/49, 1/51, 1/55
- steric bulk 1/72, 2/252
- steric demand 1/144
- steric effects 3/162
- steric interaction 1/166
- steric size 1/126
- sterically bulky alkoxides 1/181
- stiffness 3/340
- stilbene 2/259
- Stille coupling 2/298
- stock solutions 2/144
- Stoltz 2/315
- stoppering 2/101
- strain energy 1/161
- Streck 2/486
- strong π -acceptor ligands 1/68
- structural diversity 2/275
- structurally diverse compounds 2/112
- structure-activity relationship 1/201
- styrene 2/259, 2/276, 2/467
- styrene ether Ru complex 2/147
- substituents to enhance solubility 3/121
- substituted acetylene 3/389
- 2-substituted chromenes 2/155
- 5-substituted norbornene 3/73
- π -substituted olefin 2/263
- sugar-coated polymer 3/79
- sugar-substituted polymer 3/183f
- sulfides 2/274
- sulfonamide 2/36, 2/47
- sulfonyl chloride 2/389
- sulfur ylide 1/97
- sulfur-containing olefin 2/274
- sulfur-heterocycles 2/35
- sumer 3/410
- super critical CO₂ 3/157
- super *in situ* catalyst 3/362
- supermolecule 2/98
- support 1/27, 1/45
- supported chiral catalyst for olefin metathesis 2/144
- supramolecular chemistry 2/96, 2/109
- surface complex 1/192
- surface functionalized silica 3/233
- surface organometallic chemistry (SOMC) 1/191
- surface-coated 3/240
- surface-immobilized norborn-2-ene-5-yl groups 3/231
- Suzuki coupling 2/271, 2/298, 2/394, 2/495
- Suzuki-type reaction 3/230
- swainsonine 2/88, 2/159
- Swan 3/118
- syn 1/21
- syndiotactic 1/37, 2/8
- syndiotactic polymer 3/152
- Synthetic Metals* (journal) 3/121
- Szwarc 3/14
- t**
- T_g 3/145, 3/332
- t_{1/2} 3/145
- Ta carbene 3/388
- tacticity 3/145, 3/153
- tacticity splitting 3/149
- tail-tail placements of repeat units 3/93
- tail-to-tail coupling 2/261
- Takemoto 2/21
- Tamura 3/272
- tandem asymmetric ring-opening/ring-closing metatheses (AROCM/RCM) 2/228
- tandem catalysis 2/243
- tandem enyne metathesis 2/85, 2/92
- tandem mass spectrometry 1/132
- tandem metathesis 2/173
- tandem Mo-catalyzed AROM/CM 2/142
- tandem olefin isomerization/ethylene CM reaction 2/263
- tandem process 2/152
- tandem reactions 2/505
- tandem ring-closing metathesis 2/87, 2/151
- tandem ROM/CM 2/138
- tandem ROM/RCM 2/88, 2/90f
- tandem ROMP-ATRP 3/272
- tandem strategy 2/304
- tantalacyclobutane 1/12, 3/16
- tantalacyclopentane 1/12
- tantalum alkylidyne 1/174, 3/17
- tantalum ylide 1/10f
- taxoids 2/28f

- taxol 2/18, 2/27, 2/298, 2/304, 2/356
 Tayer 2/30
 Taylor 2/40, 2/473
t-butoxide ligand 1/177
 Tebbe 2/1, 2/24, 2/209, 3/8f
 Tebbe complex 1/5, 2/2
 Tebbe reagent 2/209, 2/323, 3/11
 telechelic 3/60, 3/236
 α,ω -telechelic carbosiloxane macromonomers 2/482
 telechelic material 3/414
 telechelic oligomer 3/326, 3/331
 telechelic polybutadiene 2/485
 telechelic polybutadienes, hydroxy end-functionalized 3/275
 telechelic polyethylene 3/271, 3/274
 telechelic polyisobutylene 3/266
 telechelic polymer 1/64, 2/486, 3/74, 3/89, 3/226, 3/255, 3/262
 telechelic polynorbornene 3/265
 telechelic polyoctenamers 2/485
 telechelic polyoctenamers, chlorodimethylsilane end-functionalized 3/273
 telechelic polyolefin-like material 3/279
 Telene 3/408
 Telene® 3/410
 temperature 2/7
 template 2/252
 template-directed RCM 2/96
 template-driven 2/373
 tensile modulus 3/345
 tensile strength 3/340
 tentacle-like 3/245
 tentacles 3/228
 tentacle-type 3/231
 tentagel resin-bound 2/363
 termination 3/12, 3/261f
 termination reaction 3/259
 terminator 3/383
 ternary MoOCl_4 -*n*- Bu_4Sn -EtOH catalyst 3/385
 ternary Rh catalyst system 3/382
 terpenoids 2/26
 terpyridyl ligand 3/235
tert-butylacetylene 1/54
 tertiary ether site 2/139
 tertiary siloxanes 2/135
 tetraalkyltin 1/190
 tetracyclic 2/156
 tetraene 2/95
 tetrahydrofuranes 2/472
 tetrahydropyridine 2/191
 1,1,3,3-tetramethyldisiloxane 3/326
 tetrapeptide 2/367
 tetraponerine 2/159
 tetrasubstituted olefins 2/246
 tetratetelechelic 3/255
 thermal decomposition 1/118, 1/122
 thermodynamic data 1/37
 thermodynamic equilibrium 1/199
 thermoplastic elastomer 3/256
 THF as an additive 2/140
 thiazole side 2/326
 thiols 2/274
 thiophene 3/315
 thiophene-containing substrate 3/364
 third-order nonlinear optical susceptibility 3/400
 Thorn-Csányi 3/314
 Thorpe-Ingold effect 2/36
 threefold symmetry 1/165
 $\text{Ti}(\text{Oi-Pr})_4$ 2/11, 2/21, 2/71, 2/299, 2/302
 Ticona's Topas® 3/413
 titanacyclobutane 3/15f, 3/87, 3/278, 3/286
 Titanium isopropoxide 2/363
 Tius 2/308
 tolane 2/437
 topological 1/165, 2/414
 Tosmic reagent 2/382
 total synthesis 2/287
 tough films 3/345
trans 3-hexene 1/42
trans cinnamide 2/266
trans isomer 2/251
trans olefins 2/260
trans-3-hexene 1/118
 transformation of a growing chain end 3/84
trans-fused polycyclic ethers 2/39
 transition metal catalyst 3/377
 transition metal functionality 3/82
 transition metal-based catalytic method 2/248
trans-selective CM 2/253
trans-spanning diphosphine 2/417
trans-spanning ligands 2/415
 trefoil knots 2/97
 Tri Olefin Processes 1/1
 triblock copolymer 3/272, 3/387
 triblock polymer 3/272
 tributylstannyl moiety 2/40
 triflic acid 1/19
 trifluoropropene 2/273
 triisopropylstibine 1/96
 trimethylphosphine 3/35
 1-(trimethylsilyl)cyclobutene 1/51, 2/483
 trimethylsilylcyclooctatetraene 2/483
 trimethylsilyldiazomethane 1/74

- triphenylphosphine 2/386
 (+)-triptinin A 2/16
 tris(pyrazolyl)borates 1/70
 trisaccharide 3/187, 3/208
 tris-amido molybdenum 2/79
 trisiloxane monomer 3/326
 trisubstituted 2/261
 trisubstituted olefin 2/224, 2/262, 2/304,
 2/307, 2/332, 2/357
 1,3,5-trivinylbenzene 2/469
 triynes 2/169
 tropane alkaloids 2/342
 Trost 2/178, 2/194, 2/199, 2/302, 2/310
 Trost and Carda 2/302
 (–)-tuberostemonine 2/263
 tungstacyclobutadiene 1/177, 1/179
 tungstacyclobutane 1/15, 1/19, 3/18, 3/286,
 3/301
 tungsten catalyst 3/17
 tungsten hexachloride 1/176
 tungsten-alkylidene 3/18
 tungsten-alkylidyne complex 2/78
 tungsten-carbene 3/76
 β -turn 2/57f
 two transition states 1/163
 two-dimensional ^1H NMR 3/154
 Type I olefins 2/288
 Type II olefins 2/288
 Type III olefins 2/288
- u**
 Uemura 2/26
 Undheim 2/55, 2/82, 2/170, 2/199
 unicomponent catalyst 3/379
 unimolecular micelles 3/98
 unimolecular process 1/119
 α,β -unsaturated carbonyl-containing olefin
 2/268
 unsaturated cyclic amines 2/48
 α,β -unsaturated esters 2/51
 α,β -unsaturated lactam 2/346
 unsaturated polymer 3/258
 unsaturated pyrans 2/139
 unsaturated siloxanes 2/478
 α,β -unsaturated γ -sultams 2/35
 unstrained cycloolefins 2/224
 urethanes 2/494
 user-friendly Mo-based catalysts 2/143
- v**
 van Boom 2/39, 2/157
 Van der Schaaf 1/67
 van Koten 2/96, 2/420, 2/428
 vancomycin 2/330, 3/196, 3/213f
 vancomycin-resistant 2/373
 vannusal A 2/16
 variable-density composite 3/410
 V-ATPase activity 2/306
 Verdine 2/364, 2/373
 Vestenamer[®] 3/408, 3/408
 vinblastine 2/356
 vinyl borate 2/495
 1-vinylcycloalkene 2/197
 4-vinylcyclohexene 3/267
 1-vinylcyclopentene 2/195
 vinyl epoxide 2/273
 vinyl ether 1/144, 3/277
 5-vinylnorborn-2-ene 1/142
 vinyl oxazolidione 2/266
 vinyl sulfide 3/277
 vinylcyclopropane 2/471
 vinylidioxolane 2/262
 vinyl-epoxide 2/354
 vinylic ethers 2/41
 vinylidenes 1/98, 1/102
 vinylrhodium 3/382
 vinylrhodium complex 3/389
 vinylsilane 2/463, 2/465, 2/482
 vinylsiloxanes 2/142, 2/276
 vinylsilyl alkenyl ethers 2/473
 vinyl-substituted internal alkyne 3/363
 vinylsulfone 2/273
 vinyltriethoxysilane 2/485
 vinyltrimethylsilane 3/325
 virtual recording 3/167
 vitronectin 3/211
- w**
 W($\equiv\text{C}t\text{Bu}$)($\text{O}t\text{Bu}$)₃ 1/196
 W2($\text{O}-t\text{Bu}$)₆ 1/179, 1/184
 Wagener 3/273f, 3/296, 3/313
 Wagner 2/74, 3/270
 Walters 2/22
 Wang 2/14
 Wang-bound γ -amino butyric acid (GABA)
 2/222
 Wang resin 2/221
 Wanzlick 1/80
 Warwel 2/260
 Water-soluble 3/146
 water-soluble catalyst 3/383
 water-soluble poly(1,4-phenylene vinylene)
 derivative 3/39
 water-soluble ruthenium-based catalysts
 3/55
 Watson 3/274
 WAXS spectra 3/343f
 Weiss 3/230

well-defined 3/286
well-defined ruthenium catalysts 3/44
Wender 2/299, 2/304
Werner 2/224
Werner systems 1/147
Wharton fragmentation strategy 2/29
White 2/50
Wiemer 2/52
Wilkinson's catalyst 2/170, 3/339
Williams 2/42
Winkler 2/303, 2/309
Wittig 2/379
Wittig olefination 2/267, 2/330
Wittig reaction 2/45, 2/323
Wittig-like 1/10, 1/25, 1/184, 3/313, 3/318, 3/322f
Wittig-type 3/13, 3/15, 3/228, 3/278
Wittig-type reaction 2/298, 3/84, 3/88, 3/96
Witulski 2/170
WMe₆/SiO₂ 1/196
Wood 2/26, 2/303
Wright 2/22
Wrighton 2/405

x

XANES 1/191
Xn 3/260

X-ray technique 3/341
X-type ligands 1/125

y

Yamamoto 2/46
Yao 2/36
Young 2/420
Yuzu lactone 2/443

z

Zeon 3/413
Zeonδs Zeonex® 3/413
Zeonor® 3/413
Ziegler 3/2, 3/6
Ziegler catalyst 1/1
Ziegler-Natta 1/33, 1/73, 3/312
Ziegler-Natta catalyst 3/174
Ziegler-Natta polymerization 3/87, 3/344
Ziegler-Natta-type 3/284
Zimmerman 2/109
zirconocene-catalyzed carbomagnesation 2/347
Z-olefin 2/326
Z-olefin formation 1/129
Z-olefin isomerization 2/300
Z-olefin selectivity 2/215
Zuech 2/207